## Do you think you are paying too high a price for your medicine? Do you wish more affordable options were available? Let us know!

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## Case Study: Aripiprazole
## Polar Opposite Prices for Antipsychotics

**Original Manufacturer:** Otsuka is the original manufacturer of aripiprazole, but in many countries—including South Africa— jointly markets the drug with Bristol-Myers Squibb, under the trade name Abilify.

**Generic Manufacturers:** While generic aripiprazole is not available in South Africa (see section on patents), a number of manufacturers in India produce aripiprazole, including (but not limited to) Zydus, Lupin, Ranbaxy and Sun Pharma.

**Usage:** Primarily used for the treatment of schizophrenia or bipolar disorder. Aripiprazole can also be used to treat major depression disorder.[i]

**Recommended Dosage[ii]:** Typical adult dosage ranges from 10 to 30 mg daily. For depression, adults will generally start at lower daily dosages of the drug.

**Pricing:**

- South Africa: 10mg tablet costs R35.60.[iii]
- Japan: 12mg tablet costs ¥340.70 (R34.05)[iv]. The closest quantity per unit equivalent in Japan is the 12mg tablet.
- India: At least four generics are available from manufacturers Zydus, Lupin, Ranbaxy and Sun Pharma, at an average cost per unit of R0.96 for a 10mg tablet.[v] The originator product, Abilify, is not marketed in India due to the high level of generic competition.[vi]

**→South African price per mg (R3.56/mg) is 20% higher than the Japanese price per mg (R2.84/mg).**

**→South African cost per unit for a 10mg tablet is over 35 times higher than the average generic price in India.**

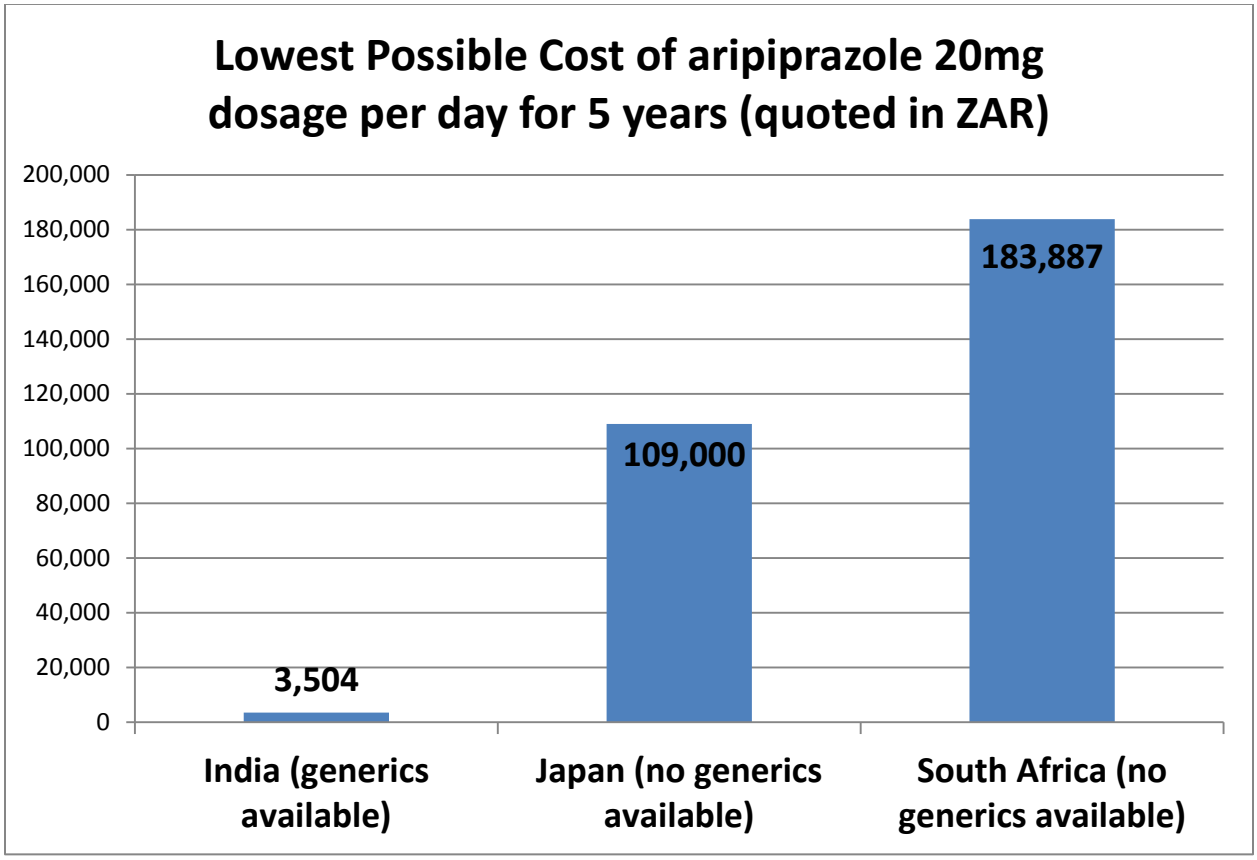
**Access Spotlight:**

Aripiprazole is one of the top ten selling drugs in the world, and in South Africa, it earned over R30million in annual revenue for BMS in the South African private sector in 2012-13. Abilify's high profitability drives Otsuka's earnings growth[vii], contributing over 30% to the company's total consolidated net sales in 2012, and the company heavily relies upon maintaining market exclusivity through patenting strategies.[viii]

The initial U.S. patent application was filed by Otsuka in October 1989. A five-year extension granted in the U.S. means the patent does not expire there until October 2014, with a pediatric indication further extending the patent until 2015.[ix] This original patent cannot be found through the the South African online patent search database, but Otsuka has filed multiple patents on carbostyril derivatives, which are similar compounds to early-stage aripiprazole.

In South Africa, a substantial number of patents have been filed on aripiprazole, by BMS and Otsuka, as well as by the companies Alkermes and Synthon.[x] Otsuka and BMS have filed applications on various process, method, and formulation patents in 2003, 2005, 2006, and 2010, with two pending applications filed in May 2013 and July 2013. While generics will soon become available in the United States, and are widely available in India, where no patents exist on the drug, patients in South Africa may have decades to wait for lower prices.

**→The graph below illustrates the prices a patient taking aripiprazole for five years would pay in the three different countries, demonstrating the significant impact that competition can have on price.**

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## Case Study: Trastuzumab
## No Low Prices In Sight for Breast Cancer Patients

**Burden of Disease:**
Breast cancer is the most common cancer among women in both developing and developed countries, and the leading cause of cancer death for women in South Africa[xi]--in 2010, global incidence was 1.64 million women, with a projected increase to as high as 2.7 million by 2030.[xii]

The South African National Cancer Registry estimates one in 33 women will develop breast cancer in her lifetime.[xiii] Approximately 15-20% of breast cancers can be treated with trastuzumab.[xiv]

**Original Manufacturer:** Genentech (member of the Roche Group); marketed by Roche in South Africa under trade name Herceptin.

**Generic (Biosimilar) Manufacturers:** None in South Africa. In India, Roche used an injunction to block sales of a biosimilar product jointly developed by Biocon and Mylan.

**Usage[xv]:** Breast cancer treatment, specifically adjuvant (early-stage) HER2+ breast cancer and metastatic breast cancer which "has spread to other parts of the body beyond the breast."[xvi]

**Standard Dosage[xvii]:** While use of the drug is dependent upon a patient's weight and how efficiently vials are fully used, a 2006-2007 study showed that the average patient used approximately **8.43 grams per year.**[xviii]

**Pricing:**
In South Africa, trastuzumab costs R24, 290.91 per 440mg vial.[xix] This is equivalent to **R55,206.61 per gram**, amounting to approximately **R465,392 per patient per annum**, or USD45,710.[xx]

In comparison to a number of other middle-income countries, South African prices are higher than those of India or Pakistan and significantly lower than those of Brazil. Surprisingly, South Africa pays more per gram for trastuzumab than several high-income countries, including Belgium and the United Kingdom.[xxi]

While Roche's international prices range from USD3,000 (R29,806) to USD9,000 per gram (R 89,418), a potential alternative supplier of trastuzumab suggests the drug could be manufactured for as little as USD31 (R308) per gram, or USD242 (R2404) per year – roughly one percent of the lowest Roche price![xxii]

Trastuzumab is so expensive that the South African public sector only provides it to clinical trial patients, or on a case-by-case basis.[xxiii] Even private medical aid schemes can refuse to cover the medicine in full, as the high price would raise the cost of premiums for all members.[xxiv] While the government is in discussions with Roche to bring down the public sector price of trastuzumab[xxv], a significantly more affordable version is unlikely to be available in South Africa in the near future —the reasons for this are explored below.

**Access Spotlight:**
Trastuzumab was developed in the 1980s and early 1990s by biotech company Genentech, in cooperation with UCLA. Clinical trials on trastuzumab initiated in 1992 and the drug received approval for the treatment of breast cancer from US and European regulatory authorities in 1998 and 2000, respectively. Roche acquired the license to market trastuzumab outside the United States in 1998.[xxvi]

Trastuzumab was patented widely in a number of countries, including South Africa. Early patent applications filed for trastuzumab date back to 1992 in some jurisdictions,[xxvii] and are nearing expiration. However, online search results of the South African patent database yield a number of later patent applications, with one filed as recently as 2013—when granted, this could extend Roche's monopoly over trastuzumab sales for an additional 20 years until 2033.[xxviii]

Roche's financial reports clearly indicate that trastuzumab is a key sales and growth driver for the company.[xxix] Roche is able to exploit the absence of trastuzamab alternatives by charging high prices for the drug, which earned it **USD6.4billion (R63.6 bn) in global sales in 2012**—this **accounted for 25% of the total oncology portfolio's sales and over 15% of total sales in Roche's Pharmaceutical Division**.[xxx] Trastuzumab's high prices also allow the company to offset the lost revenue from other drugs in its portfolio that have recently come off-patent.[xxxi]

Recent IMS Health data lists Herceptin as one of the three top-selling anti-cancer drugs in South Africa, which garners **over R100million in annual revenue for Roche, in the South African private sector alone**.[xxxii]

Trastuzumab belongs to a class of drugs called "biologics," which are made through biological, rather than chemical processes. For manufacturers trying to replicate an original biological drug, making an exact equivalent version is not feasible.[xxxiii] Instead, other manufacturers produce a "biosimilar" version, which requires them to conduct their own clinical trials to obtain accurate data on safety and efficacy. The result is that it often takes far longer for competing manufacturers to develop more affordable alternatives for biologics than it does for drugs. Companies like Roche have pursued aggressive patenting strategies with biologics to block or limit competition for extended periods of time.[xxxiv] By patenting combinations or improved formulations of a drug like trastuzumab, companies like Roche rely on having the most cutting-edge version of their product patent-protected, even when the original product goes off-patent, so that competitors' products are less appealing.

*How will fixing South Africa's patent laws help?*
One solution countries have when a patented medicine is priced out of reach, but cheaper alternatives could be made, is to issue a compulsory license. This allows a non-originator company to make a drug at a lower price, so more people have access to the medicine. The non-originator must pay a set licensing fee to the originator as compensation during the remainder of the patent period—or until the price of the original product comes down and the compulsory license is no longer necessary. In addition to improving access to expensive drugs, a compulsory license can also result in some level of technology transfer to a manufacturer in a developing country like South Africa. Over time, such technology transfer could enhance general technical skills in a company, and lead to a more robust domestic industry.

In India, the government was considering the issue of a compulsory license for trastuzumab.[xxxv] Rather Roche lowered the price of the drug in India from 110,700 rupees (USD2,000) to 75,000 rupees (USD1,366) per vial—a 31% drop.[xxxvi] While this price tag still put the drug out of reach for most Indians, it weakened the case for issuing a successful compulsory license. Without India presenting a viable threat of using a compulsory license, however, Roche may not have had any incentive to lower their price at all.

The problem for South Africa is that, due to outdated laws, the process for issuing a compulsory license is not very practical—no compulsory license has ever been issued for a pharmaceutical in South Africa. The process requires High Court proceedings, which can be expensive and time-consuming, and therefore do not respond quickly or practically to the country's health needs. A United Nations Development Programme report[xxxvii] notes that an application for a compulsory license can take up to three or more years including appeals.

At the same time the Indian government was considering a compulsory license, efforts were also underway by civil society in India to oppose a secondary patent on trastuzumab—a patent filed for a variant of the drug that would run until 2019,[xxxviii] and block generic competition after the initial patent had expired. This patent had already been revoked in Europe in 2010, increasing the likelihood of a successful challenge in India. Under increasing pressure to stop charging prices very few could afford to pay, Roche abandoned its patent in India in late 2013—though this patent is still on the books in South Africa.[xxxix] This was good news for Indian civil society, who hoped a cheaper biosimilar version of the drug would be available in early 2014, and no longer blocked from market entry.[xl] Unfortunately, the victory was short-lived.

Roche was able to ward off the threat of competition from a product jointly developed by manufacturers Biocon and Mylan, who planned to market their product in early 2014. Roche argued in court that the new product could not have undergone sufficient clinical testing—based on 2012 Indian guidelines Roche itself had helped to draft.[xli] The court ruled in Roche's favor and issued an injunction, halting the marketing plans of the biosimilar in India.

While more affordable trastuzumab biosimilars are not yet globally available, countries like India are increasingly closer to overcoming Roche's many patent barriers—and getting some of the best global prices for the Roche product in the meantime. Unlike South Africa, India has procedures for challenging patent rights that are practical to implement, and can respond relatively quickly to public health needs. Even if a cheaper Indian alternative to trastuzumab is available soon, South Africa will face significant challenges in gaining access to it—patent barriers could mean that breast cancer patients in South Africa will continue to suffer not only from their disease, but also be locked into high prices from Roche for the next 19 years.

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[iv] Price as of September 10, 2013, as found in the NHI drug list: http://yakka-search.com/index.php?scd=17&key=1179045F3026&stype=7
[v] All exchange rate as at 02 December 2013 – Bloomberg Currency Converter: http://www.bloomberg.com/markets/currencies/currency-converter/
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[xviii] *Proposal for the inclusion of trastuzumab in the WHO Model List of Essential Medicines for the Treatment of HER2-Positive Breast Cancer*, Knowledge Ecology International, University of California San Francisco, Universities Allied for Essential Medicines (UAEM) & Young Professionals Chronic Network (YP-CDN), 14 January 2013, pages 15-17 – Available here: http://www.who.int/selection_medicines/committees/expert/19/applications/Trastuzumab2_8_2_A_Ad_Final.pdf
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[xxiv] See: http://www.iol.co.za/news/south-africa/discovery-agrees-to-pay-for-herceptin-1.269423
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[xxx] Roche Finance Report 2012, page 11
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[xxxvii] At pages 61-62 available here: http://www.undp.org/content/dam/undp/library/hivaids/English/using_law_to_accelerate_treatment_access_in_south_africa_undp_2013.pdf
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