Patent barriers to medicine access in South Africa: A case for patent law reform

Publication of the Fix the Patent Laws Campaign

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Fix the Patent Laws is a joint coalition of the Treatment Action Campaign (TAC), Doctors Without Borders (MSF), SECTION27, the South African Non-Communicable Diseases Alliance (SANCD Alliance), DiabetesSA, EpilepsySA, Marie Stopes South Africa, the Stop Stock Outs Project (SSP), the South African Depression and Anxiety Group (SADAG), Cape Mental Health (CMH), the South African Federation of Mental Health (SAFMH), the Schizophrenia and Bipolar Disorders Alliance (SABDA), as well as the Cancer Alliance, including alliance members: AmaBele Belles' Project Flamingo, Breast Health Foundation, Breast Course 4 Nurses, Cancer Association of South Africa (CANSA), Can-Sir, Childhood Cancer Foundation of South Africa (CHOC), Igazi Foundation, Hospice Palliative Care Association (HPCA), Look Good Feel Better, National Council Against Smoking, Oncology Nursing Association of SA, Pancreatic Cancer Network of SA, People Living with Cancer (PLWC), Reach for Recovery, Pink Trees, The Sunflower Fund, Vrede Foundation and Wings of Hope.

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Introduction

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USEFUL TERMS

Originator

Initial versions of medicines brought to the market, generally marketed by the patent holder or a company that has a marketing agreement with the patent holder.

Small molecule medicines

Medicines whose active ingredients are chemically manufactured.

Biologic/ large molecule medicines

Medicines whose active ingredients are made or derived from living organisms. Biological products include a wide range of pharmaceutical products, such as vaccines, recombinant therapeutic proteins and monoclonal antibodies.

Generic

Follow-on versions of small molecule medicines, usually produced by companies other than the originator producing company. Generic medicines, also known as multi-source medicines, are therapeutically equivalent to and interchangeable with to originator medicines.

Biosimilar

Follow-on versions of biologic medicines, usually produced by companies other than the originator producing company. As biologic medicines are produced from living organisms, biosimilar medicines are not exactly identical to biologic medicines but are comparable in terms of safety and efficacy.

Clone

Rebranded versions of originator medicines launched by the patent holder as a generic or biosimilar product, often at a lower price than the original brand. Patent holders typically launch clones in an effort to retain market dominance when patent monopoly periods end. The Medicines Control Council defines a clone as "a duplicate application submitted by the innovator of its own product under a different proprietary name at any stage during the product life cycle".[1]

International non-proprietary name (INN)

The official non-proprietary name given to a medicine or active pharmaceutical ingredient that is unique and globally recognised. The INN is also referred to as the generic name of a medicine.

Intellectual property

Intellectual property or 'IP' rights protect creations of the mind such as inventions, designs, or literature. IP rights include patents, trademarks, copyright and designs, and others, and are not limited only to the health and medicines realm.

Patent

A patent is an exclusive right granted on an invention on a country-by-country basis, allowing its holder to exclude others from using, selling, producing, or importing that invention without the holder's permission. The invention, as it relates to pharmaceuticals, could be a product or a process. In countries that are members of the World Trade Organisation, patents are granted for 20 years dated from the time of filing (excluding least developed countries that have utilised extension periods).

TRIPS

Acronym for the "Agreement on Trade-Related Aspects of Intellectual Property Rights". TRIPS is an international agreement between members of the World Trade Organisation, regarding the standards of intellectual property protection that they will provide.

TRIPS health safeguards

Provisions and flexibilities within TRIPS that countries can adopt into national law in order to protect health and in particular, to enable generic competition to address unaffordable medicine prices.

[1] http://www.mccza.com/documents/632c3b6a947_Multiple_applications_Aug15_v2_for_comment.pdf

THE STORY SO FAR

Over the past 15 years, HIV activists in South Africa have won significant victories to secure affordable access to antiretroviral (ARV) treatment through challenging patent monopolies. The cost of a first line ARV regimen in the country has dropped by 96% since 2000. With access to affordable generic products, South Africa has been able to significantly scale-up ARV treatment to more than three million people. Despite critical victories won through battling patent monopolies on an ad hoc basis, systemic problems in South Africa's laws governing the protection of patents continue to inhibit access to medicines for all illnesses in the country.

Seeking to address these barriers, the Treatment Action Campaign (TAC), Doctors Without Borders (MSF) and SECTION27 launched the Fix the Patent Laws coalition in 2011. The coalition advocates for reform of South Africa's patent laws to address the issues that block access to affordable medicines in the country.

Since its 2011 launch, the coalition has grown to include 31 patient groups and organisations who have witnessed first-hand how shortcomings in South Africa's patent laws block access to affordable medicines for cancer, diabetes, mental health, epilepsy, other non-communicable diseases, sexual and reproductive health, HIV and TB.

In addition to the three founding organisations, coalition membership now includes: the South African Non-Communicable Diseases Alliance (SANCD Alliance), DiabetesSA, EpilepsySA, Marie Stopes South Africa, the Stop Stock Outs Project (SSP), the South African Depression and Anxiety Group (SADAG), Cape Mental Health (CMH), the South African Federation of Mental Health (SAFMH), the Schizophrenia and Bipolar Disorders Alliance (SABDA), as well as the Cancer Alliance, including alliance members: AmaBele Belles' Project Flamingo, Breast Health Foundation, Breast Course 4 Nurses, Cancer Association of South Africa (CANSA), Can-Sir, Childhood Cancer Foundation of South Africa (CHOC), Igazi Foundation, Hospice Palliative Care Association (HPCA), Look Good Feel Better, National Council Against Smoking, Oncology Nursing Association of SA, Pancreatic Cancer Network of SA, People Living with Cancer (PLWC), Reach for Recovery, Pink Trees, The Sunflower Fund, Vrede Foundation and Wings of Hope.

Following advocacy efforts by the coalition, in 2013 the South African government committed to reforming South Africa's patent laws to adopt TRIPS health safeguards in a draft National Policy on Intellectual Property. Yet three years later, little concrete action has been taken to adopt and implement reform and many critical medicines remain inaccessible to the majority of people living in South Africa who could benefit from them. In July 2016, a new IP Consultative Framework was released by the Department of Trade and Industry, but real reforms remain distant.

EXECUTIVE SUMMARY

In this report, we present nine case studies that demonstrate how systemic shortcomings in South Africa's patent laws negatively impact on access to medicines to treat a wide range of diseases in both the public and private sectors.

The case studies illustrate how a flawed system can allow pharmaceutical companies to prolong their monopoly periods in South Africa for years – and sometimes even decades – after their patent protections have expired in other parts of the world, to the detriment of millions of patients.

To prolong their periods of patent protection, companies commonly apply for multiple patents on individual medicines over time – a tactic known as evergreening. Due to shortcomings in South Africa's laws – namely, a lack of examination for patent applications – 'evergreening' occurs frequently.

The result is that South Africa's patents office grants patents that are rejected in other countries, and also grants patents that may not stand up to national patentability criteria. Additionally, patents that are overturned in other countries through opposition or legal procedures are often unchallenged or upheld by courts in South Africa.

The complexity of identifying when patent monopolies actually expire in South Africa and the conservative approach of the country's courts in ruling on patent challenges (see explanation on page 14), disincentivises generic and biosimilar companies from launching their products.

These challenges are further compounded by slow drug registration procedures in the country (see more on page 16) that can delay and disincentivise generic and biosimilar companies from bringing their products to market when patents have expired, or when a opaque patent landscape exists.

In this report we explore how ongoing patent protection and sometimes murky patent environments inhibit the use of generic

and biosimilar versions of many medicines in South Africa that are already available in other countries where patent protection was not granted, has expired, or has been overturned.

In seeking to understand how lack of access to generic and biosimilar products impacts on medicine access in the country, we have explored the accessibility of patented products in both the public and private healthcare sectors.

The vast majority of people living in South Africa, for whom private medical insurance is unaffordable and inaccessible, are dependent on the government-funded public sector for healthcare services. Only 16.2% of people living in South Africa have private insurance enabling them to access private sector care[2], which they purchase personally or receive via their employer or family members.

In exploring the accessibility of patented medicines included in our case studies, we found that medicines which remain under patent are often excluded from prescribed minimum benefits in the private sector, allowing private insurers to refuse to cover their full costs. The high costs of some patented medicines often means they are provided only under limited circumstances in the public sector, or not at all. Eight of the nine case study medicines reviewed in this report – for which generic and biosimilar products are unavailable in the country – are not procured nationally for public sector use or fully covered by private insurers. Where figures for private sector expenditure by patients and private insurers are available, the report demonstrates that huge savings could have been achieved if generic or biosimilar products (at equivalent prices to India and/or Canada) were accessible in South Africa.

In circumstances where the government and private insurers are unable to cover the high costs of medicines, it is often impossible or extremely difficult for individual patients to cover treatment costs. For these patients, lack of access to life-saving and other treatments can result in death or significantly reduced quality of life.

In this report, we hear the stories of people who are unable to – or face extreme difficulty in – accessing the medicines they need. To improve affordability and accessibility of medicines for these patients, and for all people living in South Africa, patent law reform is urgently needed.

HOW CAN SOUTH AFRICA FIX ITS PATENT LAWS TO PROTECT HEALTH?

The constitutionally guaranteed right of access to health care services supersedes patent protection, which should not come at the expense of people's lives. South Africa must better balance its patent laws in order to protect people's rights to access medicine as a priority over commercial patent rights. To achieve this, the Fix the Patent Laws coalition is advocating for South Africa to adopt a number of reforms to its patent laws, which are explained on page 11.

However, to understand the reforms that the coalition is advocating for, it's important to first understand South Africa's international obligations for protecting patents.

What are South Africa's international obligations for protecting patents?

In 1995, South Africa became a member of the World Trade Organisation (WTO). The WTO sets general standards of patent protection that all WTO members are required to provide under the Agreement on Trade-Related Aspects of Intellectual Property Rights – commonly known as the TRIPS agreement.

TRIPS requires that WTO members of a certain development status provide 20 years of patent monopoly protection on products and processes that are new, innovative and capable of industrial application, including new chemical entities used to make medicines. However, while TRIPS requires 20 years of patent protection, it includes important safeguards that countries can adopt into their national laws to ensure that patents do not block medicine access.

While South Africa's laws provide for 20-year patents as required by TRIPS, they do not include many of the safeguards allowed under TRIPS to protect public health. The Fix the Patent Laws coalition is advocating for South Africa to fully adopt into national law the public health safeguards enshrined under TRIPS, including but not limited to those explained on page 11.

[2] http://www.health-e.org.za/wp-content/uploads/2015/12/National-Health-Insurance-for-South-Africa-White-Paper.pdf

WHERE DO WE GO FROM HERE?

Since the launch of the Fix the Patent Laws campaign in 2011, the South African government has indicated its intention to fix systemic shortcomings in the country's patent laws to protect and promote medicine access.

In September 2013, the Department of Trade and Industry released a draft National Policy on Intellectual Property committing to national patent law reform to fully adopt TRIPS health safeguards. In April 2015, the Companies and Intellectual Property Commission (CIPC) announced plans to begin phasing in a patent examination system in the country, and has since started to recruit and train new patent examiners.

Despite positive commitments by government, progress toward patent law reform has been plagued by ongoing delays. Further, U.S. and European multinational pharmaceutical companies have sought to sideline adoption of health safeguards into South Africa's national patent laws. In early 2014, documents leaked to the media outlined plans of multinational pharmaceutical companies to use ZAR 6,4 million (US$ 450,000) to finance advocacy efforts to delay patent law reform. This covert plot was coined as 'Pharmagate'.

In 2015, the coalition gained significant traction, with many new members joining. In October 2015, the coalition called for South Africa's Trade and Industry Minister, Rob Davies, to publicly account for when patent law reforms would progress. In a letter to the coalition, Minister Davies recommitted to the adoption of TRIPS health safeguards in South Africa during 2016.

In July 2016, the Department of Trade and Industry released a Framework Consultation document for finalising the National IP Policy. A finalised National Policy on Intellectual Property that commits to fully integrating TRIPS health safeguards is urgently needed to balance access to medicine with the granting of intellectual property rights. Most importantly, bills seeking to fully adopt TRIPS health safeguards must be introduced in Parliament to reform the Patents Act 57 of 1978 and other health-related IP legislation. These bills should invite public submissions, hearings and parliamentary review. Establishing a substantive patent search and examination system is not contingent upon legislative reform, and the process should continue to move forward. However, this process must be done transparently with opportunity for stakeholder input to ensure that it is not corrupted by commercial interests.

The Fix the Patent Laws coalition will continue to monitor and advocate for reform of South Africa's patent laws, and the adoption of a pro-public health patent examination system that promotes access to medicines, as a critical step toward realising the Constitutional rights of people living in South Africa.

Photographer: Julia Hill

GAME-CHANGING PATENT LAW REFORMS TO SAVE AND CHANGE LIVES IN SOUTH AFRICA

1. SET STRICTER PATENTABILITY CRITERIA TO COMBAT PATENT EVERGREENING

Patent evergreening is a tactic used by pharmaceutical companies to prolong their periods of patent protection beyond 20 years and keep the prices of medicines artificially high. It involves filing patents on minor modifications to existing drugs.

Patent evergreening is common in South Africa, blocking access to more affordable generic and biosimilar products that are already available in other parts of the world.

Under TRIPS, countries can adopt strict patentability criteria to combat evergreening. This includes limiting the granting of patents on new uses of, and minor modifications to existing medicines.

A number of countries, including India, Argentina, and the Philippines, have adopted strict patentability criteria to limit patent evergreening.

South Africa should adopt strict patentability criteria in its patent laws to combat rampant patent evergreening in the country.

2. EXAMINE PATENT APPLICATIONS TO ENSURE PATENTABILITY CRITERIA HAS BEEN MET PRIOR TO THE GRANTING OF PATENTS

In order to ensure that patents are only granted on applications that meet patentability criteria, countries can adopt 'substantive search and examination systems' for assessing patent applications and granting patents.

Under a substantive search and examination system, all patent applications must be examined prior to being granted, to ensure that patentability criteria have been met.

South Africa, however, currently has a depository system, meaning patents are simply granted if the correct application forms are filed and application fees are paid – no substantive examination of applications is carried out.

The lack of substantive examination in South Africa means that patents are commonly granted that do not meet the country's (already limited) patentability criteria. A 2011 paper by the University of Pretoria reported that as many as 80% of patents granted in South Africa do not meet the country's patentability criteria.[3] A 2012 research report further revealed that South Africa grants 66% more patents than the United States and European Union on identical applications.[4]

South Africa should adopt a substantive search and examination system to ensure that patents are only granted on applications that meet patentability criteria.

3. IMPLEMENT PATENT OPPOSITION PROCEDURES

Patent offices don't always have all the information they need about a patent application to make the right decision. Sometimes mistakes are made, or a patent examiner may interpret a pharmaceutical patent application without properly considering the impact on access to medicines. To address this problem, many countries have introduced patent opposition procedures. This allows third parties – such as civil society, academics, or competitor companies – to oppose patent applications prior to, or shortly after, their approval, by submitting evidence to the patents office outlining why the patent should not be granted.

Currently the only way to challenge patents in South Africa is to file for revocation after a patent has been granted. Revocation procedures require lengthy and expensive litigation against patent holders, which are generally wealthy multinational corporations. The lack of affordable and expedited procedures for opposing patents disincentivises opposition and, as a result, many low-quality patents remain unchallenged.

South Africa should adopt affordable and efficient administrative procedures for opposing patents and the patents office must ensure transparency regarding pending applications and patents granted.

4. ADOPT MORE WORKABLE PROCEDURES FOR GRANTING COMPULSORY LICENSES

The adoption of stricter patentability criteria, substantive search and examination procedures, and opposition procedures would significantly reduce the number of undeserved pharmaceutical patents granted in South Africa. However, these safeguards are not enough to resolve access barriers occurring during legitimate patent protection periods.

TRIPS contains safeguards to ensure that legitimate patents do not prohibit access.

If medicines under patent are inaccessible due to price, supply, or other challenges, then governments can issue compulsory licenses to allow for manufacturing, importation and use of generic or biosimilar products during patent periods, under specified conditions (see sorafenib example on page 28 to learn how this has been done in India).

To date, South Africa has never issued a compulsory license on a medicine to address access barriers, in part due to overly burdensome court-based procedures required to secure this type of license in the country. The United Nations Development Programme estimates that, given burdensome procedures required, issuing a compulsory license in South Africa would take more than three years.[5]

South Africa should adopt expedited, administrative (rather than judicial) procedures to facilitate the granting of the compulsory licenses.

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[3] http://www.sajs.co.za/sites/default/files/publications/pdf/355-6888-1-PB.pdf
[4] http://www.fixthepatentlaws.org/?p=459
[5] http://www.undp.org/content/dam/undp/library/hivaids/English/using_law_to_accelerate_treatment_access_in_south_africa_undp_2013.pdf

Methodology and Context

Photographer: Roy Potterill

OUR METHODOLOGY

This report provides nine case studies of medicines used to treat various diseases, for which patents inhibit (or previously inhibited) access to generic or biosimilar products. More affordable quality-assured versions of these medicines are available outside of South Africa, where similar patent protections were not granted, have expired or been overturned. This report also highlights new medicines to treat drug resistant tuberculosis (DR-TB), for which patent barriers block manufacture and use of generic products globally.

The report explores how lack of access to generic and biosimilar products in South Africa has an impact on patients in both the public and private sectors. To assess the role of patent barriers in inhibiting access we considered the following:

1. *The availability of more affordable generic and biosimilar products in South Africa versus other countries.*
2. *The patent status of each medicine in South Africa versus other countries.*
3. *The accessibility of each of these medicines in South Africa's public and private sectors and, when available, the reasons for limited accessibility.*

More detail regarding the methodology utilised to collect data on patent status, availability and prices of generic and biosimilar products is provided under 'Data sources' on pg 53.

To assess medicine accessibility in the public sector, where the majority of people living in South Africa access care, we considered whether a medicine is procured nationally for public sector use. While national procurement is a good indicator of public sector medicine accessibility, a limitation of this method is that it does not account for provincial or facility level procurement which may allow some public sector patients to access medicines under limited circumstances. When available, this information has been included.

To assess medicine accessibility in the private sector, we considered whether or not a medicine is a prescribed minimum benefit. Prescribed minimum benefits are benefits for which private insurers must pay for treatment in full regardless of a medical scheme member's level of coverage. For chronic diseases covered as prescribed minimum benefits, medical schemes must cover the cost of treatment according to algorithms guided by public sector protocols.[6]

Photographer: Chelsea Maclachlan

Disclaimer: Compiling patent, access and pricing landscapes for medicines is a complex process, due to the lack of transparency from government-led information sources, and the tactics commonly used by pharmaceutical companies to create ambiguity within applications and hide information on pending and granted patents. Prices and patent status may also change. If you note any errors in this report, please inform fixthepatentlaws@gmail.com or claire.waterhouse@joburg.msf.org.

[6] http://www.medicalschemes.com/files/cmscript/cmscript82013_2014.pdf

"Why is it so difficult to understand whether medicines are under patent and when patent monopolies actually expire?"

By Prof Brook Baker, Northeastern University School of Law, and Prof Yousuf Vawda, University of KwaZulu-Natal School of Law.

Patents on medicines are based on very technical documents filed to differentiate the claimed new invention from prior inventions and to lay stake to an area of technology so as to exclude competitors. While patent law requires full and adequate disclosure by patentees that is sufficient to allow others skilled in the field to make an identical copy of the patented product when the 20-year patent period expires, there are many features of patent law and practice in South Africa that make it hard to know whether a particular medicine is patented, how many patents are "blocking" competitors, and when the patent monopoly period on a medicine actually expires so as to allow generic competition.

Patent evergreening and thickets resulting from the lack of substantive examination and opposition procedures

Pharmaceutical companies commonly file multiple patent applications on and around a particular medicine, both to prevent the sale of exact generic copies and to forestall other companies from trying to invent around the originator medicine. When multiple patents are granted on individual medicines, they often create patent thickets (overlapping patent rights) that prolong the life of patent monopolies beyond 20 years and make it difficult to judge when monopoly periods actually end. For example, a particular antiretroviral medicine, ritonavir, has over 800 related patents covering everything from the base active ingredient to variations of that chemical entity, to formulations, to dosages, to indicated uses for treating particular diseases, and to processes for manufacture.

In South Africa, it is particularly easy to file multiple secondary patent claims that prolong the life of patent monopolies (a tactic commonly known as patent evergreening involving filing patent claims on small changes to old medicines) because the country does not currently substantively examine patent applications to assess whether patentability criteria (the required levels of novelty, inventiveness, industrial applicability and disclosure) are met prior to the granting of patents. As each evergreening patent gets its own 20-year patent term, the length of the overall period of monopoly protection on a multi-patented medicine can be prolonged considerably by secondary patents.

Moreover, South Africa does not have opposition procedures to allow generic companies, scientists, public interest groups, individuals and others to challenge undeserving applications and patents via pre- and post-grant opposition procedures. The only mechanism to challenge patents in South Africa is through lengthy and expensive court procedures. Yet, in comparison to larger pharmaceutical markets like the US, EU and India, pharmaceutical patent litigation in South Africa is relatively rare. This is likely due to disincentives for undertaking litigation given that South Africa's pharmaceutical market is comparatively smaller than countries where patent disputes are common, and that the country's courts commonly do not apply a strict bar for patentability in their rulings (see case study 8: drospirenone and ethinyl estradiol).

Barriers to assessing when patent monopolies in South Africa actually expire

Insufficient public information and complexity of patent documents

Due to the complex technical features of patent documents, it is difficult for general readers (including public health practitioners and public interest groups) to identify within patent thickets which patents actually block the entry of generic competitors' products to the market. The lack of transparency in the current system further hinders this assessment. South Africa's public online searchable patent database does not always contain the full text of patent applications, making it difficult to look into the specific claims in order to assess the scope of protection.

Non-disclosure of INNs in patent applications

Pharmaceutical patent applicants are not required to mention the relevant international non-proprietary names (INN) of medicines in their patent applications and can file applications based purely on a diagram of a chemical structure or on an abstract manufacturing process, making it extremely difficult to pinpoint all relevant patents covering a particular medicine. Companies should be required to file patent applications under relevant INNs. In the event that a medicine's INN is not assigned prior to an application's filing, companies should be obliged to retroactively supplement the INN to their patent applications and documents within a given time frame.

Markush claims

Markush claims are broad patent claims that only disclose a general chemical structure and, if allowed by law, can cover millions of compounds based on multiple "functionally equivalent" chemical entities. Markush claims do not need to specify the actual lead compound with therapeutic functions. All the variations are not listed in the patent application making it nearly impossible to assess whether a particular chemical compound, that may be used as a medicine, might be covered or not.

Granting patents based on Markush claims masks the actual invention contained in the patent applications. Markush claims make it extremely difficult to conduct 'prior art' searches to determine whether a patent is deserved. Markush claims also potentially block research and development on, and commercialisation of, a large number of medicines. Markush claims have been criticised for being harmful to public health and failing to meet standards of disclosure required for patentability. It is therefore recommended that countries exclude Markush claims in their patentability criteria and examination guidelines.[7,8]

One study on pharmaceutical patents in South Africa revealed that Markush claims account for the largest portion of patents granted – up to 59% of pharmaceutical patents granted in one year were based on such claims.[9]

Divisional patents

Pharmaceutical companies also file divisional patent applications that include part of the subject matter claimed in a prior "parent" application. Divisional applications claim priority from the filing date of the earlier parent patent application. By dividing multiple claims into different patent applications, companies can "rescue" undeserved patent applications through the divisional filings if the original application is challenged or rejected. Divisional patents also further complicate medicine patent landscapes, as invalidating the original patent may not necessarily clear up the route for generic entry when other key technical features of production might have been covered by the divisional patents at the same time. Divisional patents create huge uncertainty for the competitors and can be misused to keep patent applications pending for a long time and make it difficult for competitors to know whether they might infringe a subsequently filed divisional patent.

It has been observed that the excessive use of divisional patent strategy by companies can impede local production of medicines by developing countries, and thus should be limited by law.[10]

Obscure drafting of patent applications

Pharmaceutical companies purposefully game the patent system by making their claims obscure, incomplete, and ambiguous precisely to make it hard for competitors to predict whether the patent would be granted or whether a court might find the patent valid or not. Clever drafters are as interested in creating a grey zone of ambiguity as much as a central zone of impenetrable exclusivity.

Conclusion

The end result of these multiple factors is that generic companies, health activists and public health practitioners in South Africa and elsewhere have a difficult time figuring out some of the most basic issues – such as whether a particular medicine is patent- protected or not, and if so which patents actually block access to generic alternatives. Paradoxically, drug companies treat their full patent landscapes as secret proprietary information – despite the fact that patents are meant to be granted on the basis of making information publically available, and that patent status information is publically administered by patent offices.

To address these challenges, South Africa should tighten its patentability criteria, allow patent oppositions, stringently examine patent applications, limit the type and scope of claims included in a single patent application, require transparent disclosure by pharmaceutical companies of all relevant patents on medicines and transparently publish full documentation of patents and applications.

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"What are the access challenges in the regulatory pathway?"

By Andy Gray, Division of Pharmacology, Discipline of Pharmaceutical Sciences, University of KwaZulu-Natal

Medicines fall into two broad categories according to their type or size of active ingredient. These categories are small molecule medicines (whose active ingredients are chemically developed) and large molecule medicines (also known as biologics; whose active ingredients are derived from living organisms).

In South Africa, all medicines have to be approved for quality, safety, and efficacy by the Medicines Control Council (MCC) before they can be marketed and used by patients. This applies equally to new medicines (originator products), which are usually patent-protected and available from only one source, and to follow-on (multisource) products that enter the market after patent expiry, patent revocation or when licensed by the patent holder. Follow-on products of small molecule medicines are referred to as generic medicines. Follow-on products of large molecule medicines are referred to as biosimilar medicines.

Generic medicines must be bioequivalent in order to be registered by the MCC, and are interchangeable with originator products. The law requires anyone dispensing a prescription to offer to substitute a lower-priced generic when an originator product is prescribed. Registration and sale of generic products typically leads to significant price reductions due to increased competition. When medicines are more affordable, more people have access to them.

However, there are a number of challenges that contribute to delays in registering medicines in South Africa. Preparing a complete dossier with the required information for registration of a medicine can be challenging, especially for smaller firms or new entrants into the market. There is also a significant backlog of registration applications at the MCC. It has been argued that the registration backlog at the MCC is related to the implementation of "pro-generic policies", without consideration of the resource demands created by these policies.[11,12] To address current backlogs and prevent their recurrence, important policies to promote the registration of generic products should be coupled with adequate resources for implementation, and a better prioritisation process.

Biologic medicines present their own specific registration and access problems. Many of these medicines are very highly priced, and so the registration of biosimilars at more affordable prices is eagerly anticipated. However, even though the MCC has a guideline for the registration of biosimilars and is expected to follow a process similar to that in Europe where a number of biosimilars have been registered, none have yet been approved in South Africa.[13]

To facilitate registration and use of biosimilar products, South Africa should improve the transparency of its regulatory decisions on all medicines, including biosimilars, and make them searchable online. For biosimilar products, the regulatory decisions should also provide arguments on comparability and interchangeability to the reference products. Furthermore, under South Africa's current law, biosimilars are not defined as interchangeable with the originator, which will likely limit their use following registration and should be reviewed.

While many of the above factors overlap and contribute to registration delays, fortunately South Africa's Medicines and Related Substances Act avoids the pitfall (experienced by some other countries) of patent linkage.[14] The MCC is also not hampered by data exclusivity[15] provisions, which can significantly delay the consideration of applications for follow-on generics or biosimilars.

The Medicines and Related Substances Act has been amended twice (in 2008 and 2015) to comprehensively change the decision-making process for medicines approval. Instead of relying on external Council members, decision-making in the proposed South African Health Products Regulatory Authority (SAHPRA) will be vested in the full-time staff. SAHPRA is expected to charge pharmaceutical manufacturers far higher fees for applications to register a medicine; these additional resources are expected to address many of the reasons for the current backlog.

The Amendment Acts have been passed by Parliament, and assented to by the President. They need to be carefully brought into effect, together with new regulations and guidelines. This is expected to occur in 2017.

As South Africa reviews and reforms its Patent Laws it will remain necessary to advocate against the adoption

of any provisions that would delay the authorisation of follow-on medicines in the country (such as patent linkage or data exclusivity). As South Africa implements amendments to the Medicine and Related Substances Act, it will be important to advocate for the greatest possible degree of transparency in the operations of SAHPRA, so that the new authority can be held accountable for its performance.

Bioequivalent

Bioequivalent medicines are pharmaceutically equivalent or pharmaceutically alternative medicines that have met pre-specified standards of bioavailability. Pharmaceutically equivalent medicines are medicines that are the same in terms of active ingredient and dosage form (strength, route of administration). Pharmaceutically alternative medicines are the same in terms of active ingredient but may differ in terms of chemical form (salt or ester) or dosage form, but are intended to be administered by the same route. Companies seeking registration of generic (multisource) products must submit data to the MCC to demonstrate interchangeabilty with the originator product. These data may be non-clinical, or in some cases require bioequivalence studies.

Comparable

Comparable biological medicines are similar in terms of safety and efficacy (how the medicine works). Companies seeking registration of a biosimilar product must submit clinical and non-clinical data to the MCC to demonstrate comparability to the originator product.

Interchangeable

Interchangeable medicines can be automatically substituted by pharmacists or other dispensers. Under South Africa's current laws, medicines must be bioequivalent or therapeutically equivalent to be interchangeable.

[11] Leng HMJ, Sanders D, Pollock AP. Pro-generics policies and the backlog in medicines registration in South Africa: Implications for access to essential and affordable medicines. GaBI J 2015; 4(2): 58-63.
[12] Leng HMJ, Pollock AM, Sanders D. The impact of the Medicines Control Council backlog and fast-track review system on access to innovative and new generic and biosimilar medicines of public health importance in South Africa. S Afr Med J 2016; 106(4): 350-353.
[13] Medicines Control Council. Biosimilar medicines: Quality, non-clinical and clinical requirements. August 2014. Accessible at http://www.mccza.com/documents/d259816c2.30_Biosimilars_Aug14_v3.pdf
[14] Patent linkage involves linkage of regulatory approval of medicines to patent status. In other words, patent linkage prevents registration of follow on products during patent periods.
[15] Data exclusivity seeks to prevent medicine regulatory authorities from using clinical trial data of originator medicines for the registration of generic and biosimilar products during the period of exclusivity.

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Medicine case studies

Photographer: Sydelle Willow Smith

CANCER

CASE STUDY 1: TRASTUZUMAB

For the majority of women with HER-2-positive breast cancer, life-saving trastuzumab is unaffordable. Patent monopolies could block the use of more affordable biosimilar products in the country until 2033.

What is trastuzumab used for?

Trastuzumab is recommended as an essential medicine by the World Health Organisation.[16] Trastuzumab is a biologic medicine that is used to treat human epidermal growth factor receptor 2 (HER-2) positive breast cancer and some types of stomach cancer. In combination with other drugs, trastuzumab has been shown to improve overall survival rates of women with HER-2 positive breast cancer by 37%.[17]

What are the rates of HER-2-positive breast cancer in South Africa?

Breast cancer is the leading form of cancer affecting women in South Africa, with an estimated 1 in 36 women developing the disease in their lifetime.[18] Generally between 20–30% of breast cancer patients are HER-2-positive – a type of cancer associated with a more aggressive disease, a higher recurrence rate, and increased mortality.[19]

How available is trastuzumab in the public and private sectors?

Trastuzumab is not currently purchased on national tender for use in South Africa's public sector. [1] At present, public sector access to trastuzumab is extremely limited and requires a case review by a health facility's Pharmaceutical and Therapeutics Committee, which may – and often will – reject a patient's motivation for the drug, based on cost.

Private insurers in South Africa are not required to cover the full cost of trastuzumab for patients seeking care in the private sector, as it has been excluded from prescribed minimum benefits due to its high cost. [9]

How do patents impact on price and access?

Patent monopolies held by Roche and Genentech (which provides exclusive marketing rights to Roche) in South Africa could block the use of biosimilar products in the country until 2033. [3] Patent monopolies on trastuzumab have been overcome in a number of other countries, such as India and the UK, where the patent has expired or been withdrawn by the patent holder, or through successful opposition procedures, opening the door to more cost-effective biosimilar products.

The composition patent concerning the production of trastuzumab[20] has been withdrawn by Roche in India following threats of compulsory licensing,[21] but remains valid in South Africa and will expire in 2020. In addition, Genentech also holds a patent in South Africa on the composition and formulation of trastuzumab by using antibodies[22], which could block access to biosimilar trastuzumab in the country until 2027.[23]

A number of secondary patents concerning trastuzumab granted in South Africa pose further challenges to accessing more affordable products in the country. For instance, Genentech holds a patent covering combinations of trastuzumab and other chemotherapeutic agents[24], which could block any pre-

[16] World Health Organisation. 'WHO moves to improve access to lifesaving medicines for hepatitis C, drug-resistant TB and cancers'. 8 May 2015. Available at: http://www.who.int/mediacentre/news/releases/2015/new-essential-medicines-list/en/

[17] Perez E, Romond E, Vera Suman, Jeong JH et al. Trastuzumab Plus Adjuvant Chemotherapy for Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: Planned Joint Analysis of Overall Survival From NSABP B-31 and NCCTG N9831. American Society of Clinical Oncology October 20, 2014, doi:10.1200/JCO.2014.55.5730

[18] Vorobiof, D. A., F. Sitas, and G. Vorobiof. "Breast Cancer Incidence in South Africa." Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 19, no. 18 Suppl (September 15, 2001): 125S – 127S.

[19] Mitri Z, Constantine T, O'Regan R. The HER-2 Receptor in Breast Cancer: Pathophysiology, Clinical Use, and New Advances in Therapy. Chemotherapy Research and Practice. 2012;2012:743193. doi:10.1155/2012/743193.

[20] Genentech, Inc US 60/084,459 filed May 6, 1998 equivalent to PCT/US1999/009637,(WO1999057134)PROTEIN PURIFICATION BY ION EXCHANGE CHROMATOGRAPHY equivalent to Indian patent application IN/PCT/2000/00391/KOL granted on April 5, 2007 (IN205534) set to expire in 2020 but withdrawn under threat of CL and pressure from civil society by Roche in August 2013. The EPO shows the equivalent of PCT/US1999/009637 as ZA200005879

[21] Ref. http://www.reuters.com/article/us-roche-herceptin-india-idUSBRE97F08220130816

For bracket references please see page 53.

TABLE 1: PRICES OF TRASTUZUMAB IN SOUTH AFRICA AND INDIA

DOSAGE AND FORMULATION	PRICES OF ORIGINATOR PRODUCTS IN SA PRIVATE SECTOR [2]	PRICES OF ORIGINATOR PRODUCTS IN SA PUBLIC SECTOR [1]	PRICES OF ORIGINATOR PRODUCT IN INDIA [11]	PRICES OF CLONE PRODUCT IN INDIA [11]	PRICES (IN ZAR) OF BIOSIMILAR PRODUCT IN INDIA [11]
440 mg vial ++	ZAR 55.20 US$ 3.90	Unknown	ZAR 60.71 US$ 4.29	ZAR 30.70 US$ 2.17 (Roche/Emcure)	ZAR 17.22 US$ 1.22 (Biocon/Mylan)
440 mg vial +	ZAR 24,290.00 US$ 1,717.82	Unknown	ZAR 26,723.00 US$ 1,889.89	ZAR 13,524.00 US$ 956.44 (Roche/Emcure)	ZAR 7,576.00 US$ 535.79 (Biocon/Mylan)
150 mg vial ++					ZAR 18.75 US$ 1.32 (Biocon/Mylan)
150 mg vial +					ZAR 2,813.00 US$ 198.94 (Biocon/Mylan)

+ price per single vial ++ price per single mg

clinical work until 2030 for a biosimilar trastuzumab emtansine combination (currently sold under the brand name Kadcyla, which is used to treat late stage HER-2-positive metastatic breast cancer).

Some of the secondary patents granted in South Africa have been revoked or withdrawn in other countries. For instance, Genentech holds a dosage patent[25] covering a lower dose of trastuzumab, which was opposed by six competitor companies and revoked by the European Patent Office,[26] and invalidated by the Court of Appeal in the UK for lacking inventive steps.[27] The same patent remains upheld in South Africa and could potentially block the use of the reduced dose regimen of the medicine until its expiration in 2022. Another patent concerning reduced doses of trastuzumab emtansine[28] that has been withdrawn in European Patent Office, but remains valid in South Africa, may block the use of the recommended lower dose biosimilar trastuzumab emtansine (Kadcyla) in the country until 2033.

Prices of trastuzumab

In South Africa, only Roche's branded versions of trastuzumab are available, sold under the names Herceptin and Herclon. In the private sector, a 12-month course of Herceptin costs approximately ZAR 485,800 (US$ 34,356), or more if higher dosing is required. Roche offers a lower price for its Herclon product in the public sector – although this price remains confidential. Trastuzumab emtansine is not yet available in the country.

In India, where patent protection on trastuzumab has ended, Biocon has registered a trastuzumab product which is marketed at approximately ZAR 151,520 (US$ 10,715) for a 12-month course of treatment – although this product has not yet been registered by a stringent regulatory authority.

What did the patent holder earn in 2013/2014?

During 2013, Herceptin was one of the three top-selling anti-cancer drugs in South Africa, and earned Roche more than ZAR 100 million (US$ 7.07 million) in annual revenue. [5] Between 2013 and 2014, Herceptin moved from the fifth to the second highest driver of expenditure on medicines in the private sector. [5] Globally, Roche earned US$ 6.48 billion from the sale of Herceptin during 2014.[29]

How could reforming South Africa's patent laws improve access to trastuzumab?

As competitors' biosimilar products enter the market in countries where trastuzumab patents are no longer in force, prices should fall as a result of increased competition. Yet South Africa may miss out on these price reductions given the ongoing patent monopolies granted. If South Africa had an examination system and opposition procedures in place, then it is likely that some of the ongoing patents on trastuzumab would not have been granted or would have been challenged, allowing for the use of more affordable biosimilar products following their registration.

[22] ZA2007/01234, PCT/US05/025084
[23] https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2006033700&redirectedID=true
[24] ZA2010/06186, PCT/US2009/036608. See. https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2009117277&recNum=1&maxRec=&office=&prevFilter=&sortOption=&queryString=&tab=PCT+Biblio
[25] ZA2002/01229, PCT/US2000/023391
[26] https://register.epo.org/application?number=EP00959423&lng=en&tab=main. The case is under appeal.
[27] http://www.eplawpatentblog.com/eplaw/2015/03/uk-hospira-v-genentech.html#more
[28] ZA2013/03611, PCT/US11/063764. See. https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2012078771&recNum=1&maxRec=2&office=&prevFilter=&sortOption=Pub+Date+Desc&queryString=ALL%3A%28PCT%2FUS11%2F063764%29&tab=PCT+Biblio
[29] http://www.pmlive.com/top_pharma_list/Top_50_pharmaceutical_products_by_global_sales#

TABLE 2: PATENTS GRANTED ON TRASTUZUMAB IN SOUTH AFRICA

PATENT TITLE	PATENT HOLDER	CIPC NUMBER	LODGING DATE	GRANT DATE	EXPIRY DATE	LEGAL STATUS	PCT NUMBER
PROTEIN PURIFICATION BY ION EXCHANGE CHROMATOGRAPHY	Genentech Inc.*	2000/05879	20-Oct-2000	22-Oct-2001	20-Oct-2020	Granted	PCT/US99/09637
DOSAGES FOR TREATMENT WITH ANTI-ERBB2 ANTIBODIES	Genentech Inc.	2002/01229	13-Feb-2002	25-Jun-2003	13-Feb-2022	Granted	PCT/US00/23391
HER-2 ANTIBODY COMPOSITION	Genentech Inc.	2007/01234	2-Feb-2007	31-Dec-2008	2-Feb-2027	Granted	PCT/US05/025084
COMBINATIONS OF AN ANTI-HER-2 ANTIBODY-DRUG CONJUGATE AND CHEMOTHERAPEUTIC AGENTS, AND METHODS OF USE	Genentech Inc.	2010/06186	30-Aug-2010	30-Nov-2011	30-Aug-2030	Granted	PCT/US09/036608
TREATMENT OF HER-2-POSITIVE CANCER WITH PACLITAXEL AND TRASTUZUMAB-MCC-DM1	Genentech Inc.	2013/03611	17-May-2013	30-Jul-2014	17-May-2033	Granted	PCT/US11/063764

*Genentech Inc. have a marketing agreement with Roche for the sale of trastuzumab

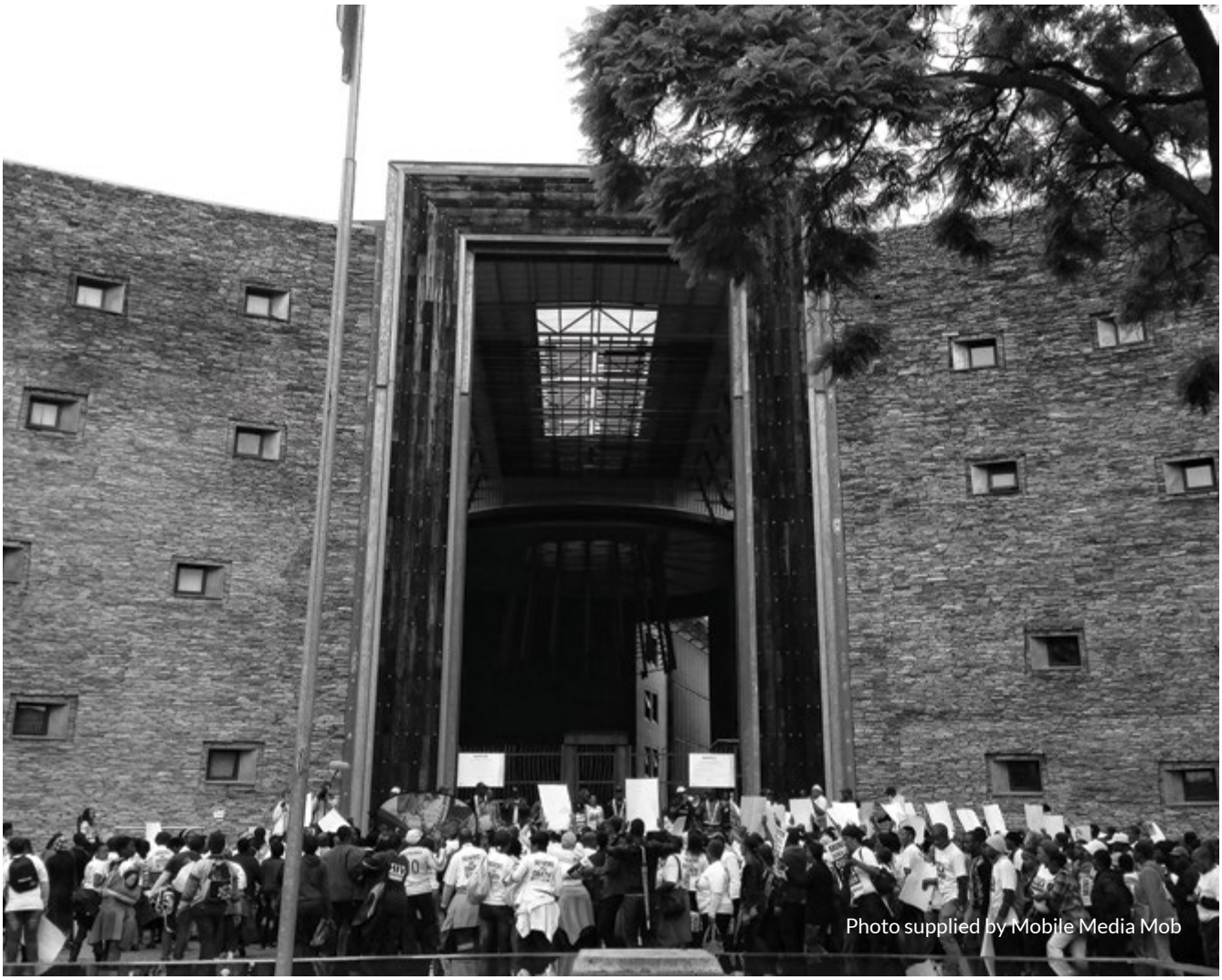

Photo supplied by Mobile Media Mob

“If I can get this treatment I can live longer, see my two sons growing”

Tobeka Daki was diagnosed with HER2-positive breast cancer in 2013. In 2014, she was told by her oncologist that she needed trastuzumab. At the time of her diagnosis, Tobeka had private health insurance, but her medical scheme told her she wasn’t covered to receive this treatment. While coping with cancer, she wasn’t able to work and subsequently lost her medical aid.

Photographer: Laura Lopez Gonzalez

“My name is Tobeka Daki. I am living in Mdantsane, Eastern Cape. I have two sons. I was diagnosed with breast cancer on the 13 November 2013.

On the TV show Isidingo, I saw Lerato who was a breast cancer survivor. When I saw her symptoms, I realised that maybe there was something wrong with me. I went to the doctor who examined me and referred me to one of the specialists. I did a mammogram and biopsy.

I went for surgery on 20 November 2013. After my surgery I had chemo for six months. Then I had radiation for six weeks. In March 2014 I was told by my oncologist that I am supposed to get Herceptin. My doctor and I applied to my medical aid but unfortunately it was declined. They claimed that the medicine was too expensive for them to cover.

In December I resigned from my job because I started getting really ill and I was scared that I might never recover again. So I chose to stay at home so that I could recover fully. Unfortunately when I left work, I stopped my medical aid as well. Now that I’m using a public hospital, the doctor hasn’t mentioned Herceptin to me again.

When I spoke to the ladies in my breast cancer support group – who are also receiving treatment in the public sector – about Herceptin, none of them had even heard of it. I was lucky just to be told.

I strongly believe that if I can get this treatment I can live longer, see my two sons growing, see my grandson growing. I think government should provide Herceptin to every woman living with HER-2-positive breast cancer so that we can live longer lives and not a scary life like the life I’m living now. Even if have a headache, I get scared that the cancer is coming back. I don’t think I am fully cured without the treatment that I was supposed to get.”

This story has been edited for length and clarity from the transcript of an interview conducted with Tobeka Daki on 16 October 2015. Following the interview, Tobeka was informed that the cancer had spread to her spine and that she would need to restart chemotherapy and radiation.

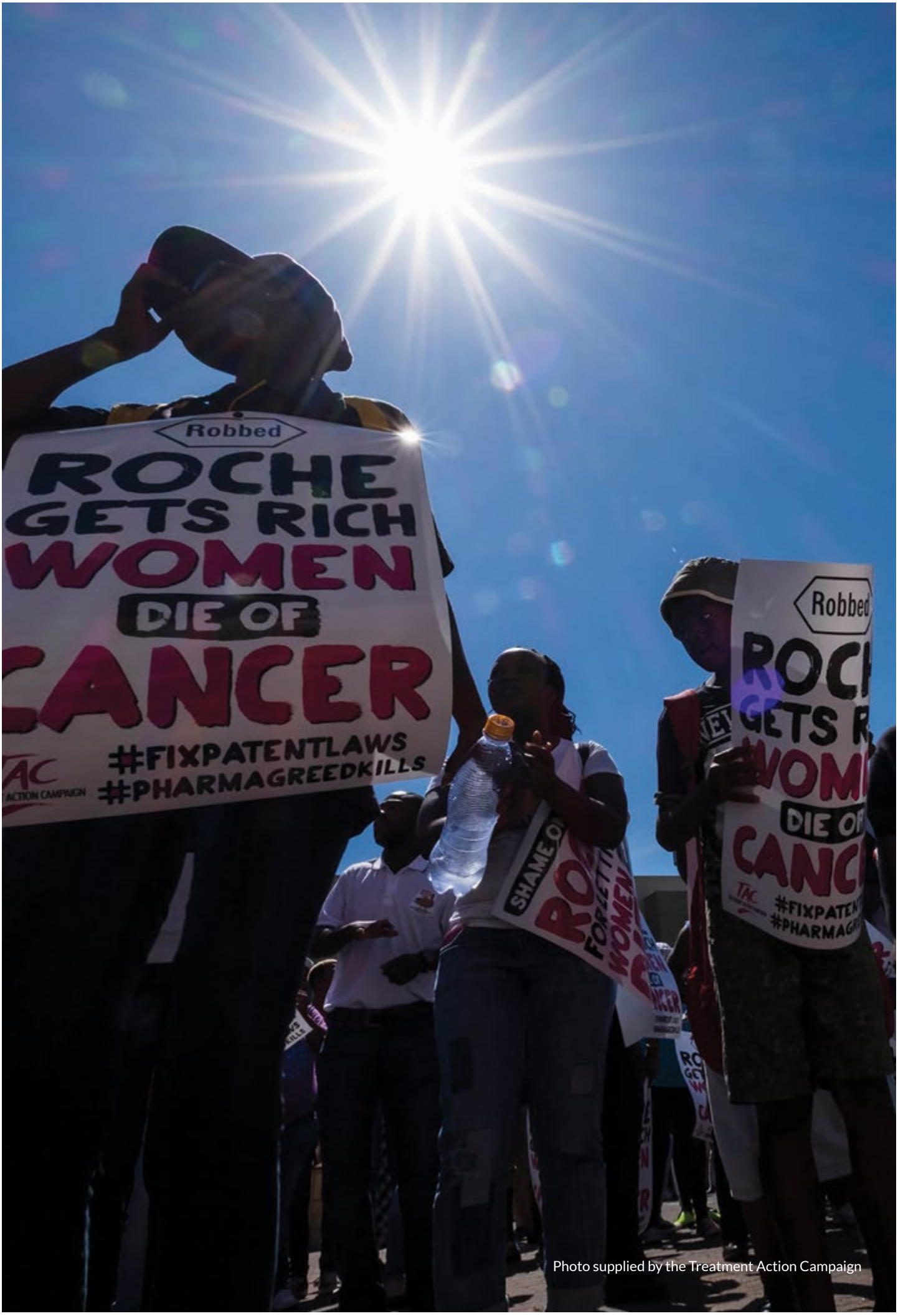

Photo supplied by the Treatment Action Campaign

Spotlight on India's battle for access to more affordable trastuzumab

The Campaign for Affordable Trastuzumab (CFAT) was launched in India in 2012 to highlight the exorbitant prices charged by Roche in India for patented trastuzumab. Public pressure led the Indian government to consider granting a compulsory license to allow for manufacturing and use of biosimilar products.[30]

Facing rising pressure from both CFAT and the Indian government, Roche established a partnership with Emcure Pharmaceuticals in 2012 to market a more affordable rebranded originator[31] of trastuzumab in India.[32,33] However the lower price offered by Emcure and Roche for its rebranded originator product was insufficient to make the drug affordable.

Patent barriers preventing the manufacture and use of biosimilar trastuzumab in India were removed in 2013, after pending and granted patents were dismissed by the patent office and withdrawn by Roche in the face of calls for compulsory licensing (read more on page 18).

India's medicines regulatory authority approved the first biosimilar version of trastuzumab in November 2013 – jointly marketed by Biocon and Mylan as Hertraz. Hertraz was introduced in India at 70% lower prices than charged by Roche for patented trastuzumab, and 45% lower prices than charged by Emcure and Roche for their rebranded originator product.

Following the launch of Hertraz, Roche filed for an injunction to prevent Biocon from marketing their biosimilar product – claiming that Biocon's package inserts infringed Roche's copyright and that Biocon should not be allowed to claim that their drug is trastuzumab.[34]

The court passed a very ambiguous order, which CFAT opposed for extending proprietary rights to the non-proprietary term "trastuzumab", which is a chemical name without any intellectual property protection. CFAT further highlighted that the ruling creates a worrying precedent for data exclusivity (see page 17), which is not provided for under India's law or required under TRIPS.

Taking advantage of the differences between the European and the Indian regulatory pathways for registering biosimilars, Roche has further challenged the registration of Biocon's product by India's medicines regulatory authority.[35] Court proceedings are currently ongoing but the court has not prevented Biocon and Mylan from continuing to market their biosimilar product in India at much more affordable prices than provided by Roche.

[30] http://www.biosimilarnews.com/india-to-issue-compulsory-license-for-herceptin
[31] The term used in India to describe a rebranded version of the originator product, often launched at a lower price, is 'rebranded originator'. In South Africa the term used to describe this type of product is 'clone'. See the Medicine Control Council's definition of clone products on page 7.
[32] http://www.fiercepharmamanufacturing.com/story/indias-emcure-manufacture-roches-herceptin-mabthera/2012-03-05
[33] http://www.ipwatchdog.com/2013/08/21/compulsory-licenses-and-statements-of-working-in-india-2/id=44761/
[34] http://infojustice.org/archives/32146
[35] http://www.gabionline.net/Biosimilars/News/Biocon-and-Mylan-challenge-Indian-ban-on-trastuzumab-similar-biologics

Member of the Delhi Network of Positive People protesting pressure from multinational pharmaceutical corporations on the Indian government to water down policies and laws that promote and protect generic competition in life saving medicines.

Photo supplied by DNP+

CASE STUDY 2: BORTEZOMIB

Pending and granted secondary patents could block access to generic bortezomib until 2035. Generic versions of bortezomib are available in India at prices 75% lower than those charged for the originator product in South Africa.

What is bortezomib used for?

Bortezomib is used to treat multiple myeloma, which is a cancer of plasma cells found in bone marrow. Several trials have demonstrated that bortezomib-based combination treatments result in higher overall survival rates for patients with multiple myeloma.[36, 37]

What are the rates of multiple myeloma in South Africa?

The number of deaths recorded in South Africa due to multiple myeloma have been observed to be on the rise in recent decades.[38] In 2008, nearly 300 cases of multiple myeloma were diagnosed in South Africa.[39]

How available is bortezomib in South Africa's public and private sectors?

In South Africa, bortezomib is not procured for use in the public sector, and is not available to public sector patients under any circumstances. [1] Private insurers are not required to cover the full cost of this treatment as a prescribed minimum benefit, as it exceeds the level of care provided in public facilities. [9]

How do patents impact on access?

In South Africa, only Janssen Pharmaceuticals' originator version of bortezomib is marketed, sold under the brand name Velcade. Millennium Pharmaceuticals (which has a commercialisation agreement with Janssen for marketing bortezomib outside of the US) holds patents on bortezomib. Millennium Pharmaceuticals was acquired by Takeda Pharmaceuticals in 2008.[40]

The initial patent on bortezomib granted in South Africa expired in 2015.[41] Millennium Pharmaceuticals holds a patent concerning bortezomib ester* in South Africa until 2030.[42] The same patent remains pending in India[43] but has not blocked the manufacture and use of generic products in the country to date. Another application on bortezomib ester remains pending in South Africa, which, if granted, would only expire in 2035.[44] Patenting esters of basic compounds is a common evergreening strategy pursued by pharmaceutical companies, but may not block generic competition if competitor companies can design around the scope of protection. Restricting evergreening tactics in South Africa could rule out such applications and improve certainty for generic entry. For instance, patent applications on esters would likely be rejected in India where strict patentability criteria have been adopted into national law.

What did the patent holder earn in 2013/2014?

In South Africa, Janssen's originator version of bortezomib is one of the top 50 products driving private insurers' expenditure on medicines. [6] Globally, Janssen and its marketing partners generated US$ 2,8 billion from the sale of Velcade during 2013.[45]

How could reforming South Africa's patent laws improve access to bortezomib?

If South Africa reformed its laws to adopt stricter patentability criteria, as well as examination and opposition procedures to ensure that patents were only granted on applications meeting patentability criteria, then it is likely that the ongoing patents on bortezomib would not have been granted removing uncertainty regarding ongoing patent barriers to allow for earlier availability of more affordable generic products in the country.

[36] http://link.springer.com/article/10.2165%2F00003495-200969070-00006
[37] http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2007.06585.x/full
[38] http://www.ncbi.nlm.nih.gov/pubmed/6710255
[39] http://www.cansa.org.za/files/2015/01/Fact-Sheet-Multiple-Myeloma-January-2015.pdf
[40] https://en.wikipedia.org/wiki/Millennium_Pharmaceuticals
[41] ZA1995/09119. Equivalent to PCT/US1995/014117, https://patentscope.wipo.int/search/en/detail.jsf?docId=WO1996013266&recNum=1&tab=NationalPhase&maxRec=&office=&prevFilter=&sortOption=&queryString=
[42] ZA2010/09177, WO/2009/154737, PCT/US2009/003602. Information available from: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2009154737&recNum=2&office=&queryString=ALL%3A%28PCT%2FUS09%2F003602%29&prevFilter=&sortOption=Pub+Date+Desc&maxRec=2. The equivalent CIPC patent number: ZA 2010/09177 and ZA2011/09368, has been granted in South Africa and will be expired in 2030 and 2031 respectively.
[43] The equivalent India application of patent cited above numbered: 107/DELNP/2011, remains pending.
[44] The CIPC patent application number ZA 2015/04133, which might be a divisional patent application of the ZA2010/09177, remains pending in South Africa.
[45] http://www.pmlive.com/top_pharma_list/Top_50_pharmaceutical_products_by_global_sales

* Esters, ethers and salts are modifications to the physico-chemical properties of known compounds, that are generally derived from undertaking known processes. It is therefore recommended that esters, ethers and salts are excluded from patentability as they do not demonstrate adequate novelty and inventiveness to receive patent protection: http://apps.who.int/medicinedocs/documents/s21801en/s21801en.pdf

TABLE 3: PRICES OF BORTEZOMIB IN SOUTH AFRICA AND INDIA

Generic versions of bortezomib are available in India at prices 75% lower than those charged for the originator product in South Africa. [11]

DOSAGE AND FORMULATION	PRICES OF ORIGINATOR PRODUCTS IN SA PRIVATE SECTOR [2]	PRICES OF ORIGINATOR PRODUCTS IN SA PUBLIC SECTOR [1]	PRICES OF GENERIC PRODUCTS IN INDIA [11]	PRICES OF ORIGINATOR PRODUCT IN INDIA [11]
3.5mg/ml vial ++	ZAR 4,178.70 US$ 295.52	Not procured	ZAR 1,079.22 US$ 76.32 (Natco, Glenmark)	ZAR 3,692.87 US$ 261.16
3.5mg/ml vial +	ZAR 14,625.46 US$ 1,034.33		ZAR 3,777.27 US$ 267.13 (Natco, Glenmark)	ZAR 12,925.00 US$ 914.07
2mg/ml vial ++			ZAR 1,338.33 US$ 94.64 (Natco, Glenmark)	
2mg/ml vial +			ZAR 2,676.66 US$ 189.30 (Natco, Glenmark)	

+ cost per vial ++ cost per mg

TABLE 4: EXAMPLES OF PATENTS GRANTED ON BORTEZOMIB IN SA

PATENT TITLE	PATENT HOLDER	CIPC NUMBER	LODGING DATE	GRANT DATE	EXPIRY DATE	LEGAL STATUS	PCT NUMBER
BORONIC ESTER AND ACID COMPOUNDS, SYNTHESIS AND USES	Millennium Pharmaceuticals	1995/09119	27-Oct-1995	31-Jul-1996	27-Oct-2015	Granted	PCT/US1995/014117
BORONATE ESTER COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS THEREOF	Millennium Pharmaceuticals	2010/09177	21-Dec-2010	28-Mar-2012	21-Dec-2030	Granted	PCT/US09/003602
BORONATE ESTER COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS THEREOF	Millennium Pharmaceuticals	2011/09368	20-Dec-2011	30-Oct-2013	20-Dec-2031	Granted	N/A
BORONATE ESTER COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS THEREOF	Millennium Pharmaceuticals	2015/04133	08-Jun-2015	N/A	8-Jun-2035	Pending	N/A

Photo supplied by Mobile Media Mob

CASE STUDY 3: SORAFENIB

The cost of a month's treatment of sorafenib in South Africa's private sector is ZAR 26,252 (US$1,856). Generic versions in India are available, thanks to a compulsory license issued in 2012, at 94% lower prices than those charged by Bayer for the originator product in SA. Sorafenib is not available in the public sector due to its high cost.

What is sorafenib used for?

Sorafenib is an oral multikinase inhibitor indicated for the treatment of advanced kidney, liver and thyroid cancer. Sorafenib has been shown to have a predictable and manageable safety profile, as well as important survival benefits.[46]

What are the rates of kidney, liver and thyroid cancer in South Africa?

The most recent South African National Cancer Registry Report recorded 409 new cases of kidney cancer, 405 new cases of liver cancer, and 307 new cases of thyroid cancer diagnosed in 2007.[47] Worldwide, primary liver cancer is the third leading cause of cancer death[48] in a single year, while kidney cancers account for about 2% of all cancers diagnosed globally.[49]

How available is sorafenib in South Africa's public and private healthcare sectors?

Sorafenib is not procured nationally for use in the public sector in South Africa given its high cost, and it is not available to public sector patients under any circumstances. [1] In the private sector, private insurers are not required to fully cover the cost of sorafenib as it exceeds the level of care provided in public facilities. [9]

How do patents impact on access to sorafenib?

Only Bayer's originator version of sorafenib, marketed under the brand name Nexavar, is available in South Africa. [1,2] Patent monopolies held by Bayer could block the use of generic sorafenib in South Africa until 2027. [3] Generic versions of sorafenib have been available in India since 2012, when a compulsory license was issued allowing for their use. The same patent upon which India has granted a compulsory license remains valid in South Africa, lasting until 2021.[50]

How much did the patent holder earn in 2013?

During 2013, Bayer generated US$ 1.06 billion from the sale of Nexavar globally.[51] In response to India's issuance of a compulsory licence on sorafenib in 2012, Marijn Dekkers, CEO of Bayer stated that the cancer drug was not developed for poor patients in India, but rather "for western patients who can afford it".[52]

How could reforming South Africa's patent laws improve access to sorafenib?

South Africa has never issued a compulsory license on a medicine, in part because the procedures for doing so are expensive and time consuming. If South Africa reformed its process for granting compulsory licenses, then compulsory licensing could be used as an expedited mechanism to access more affordable generic sorafenib in the country. Further, if South Africa reformed its laws to adopt stricter patentability criteria, as well as examination and opposition procedures to ensure that patents were only granted on applications meeting patentability criteria, then it is likely that secondary patents prolonging Bayer's period of patent monopoly would not have been granted. As a result patients in South Africa would have earlier access to generic medications at costs closer to those paid in India, which are almost 20 times less expensive.

[46] Retrieved from http://reference.medscape.com/drug/nexavarsorafenib-342260
[47] http://www.nioh.ac.za/assets/files/NCR_Final_Tables_2007.pdf
[48] http://www.hepb.org/professionals/hepb_and_liver_cancer.htm
[49] Lindblad, P. and Adami H.O, Kidney Cancer, in Textbook of Cancer.
[50] See granted compulsory license at: http://keionline.org/sites/default/fles/sorafenib_nexavar_compulsory_License_12032012.pdf . The patent under the compulsory license concerns PCT/US2000/000648. The equivalent CIPC patent ZA2001/05751 remains granted in South Africa.
[51] http://www.fiercepharma.com/story/bayers-nexavar-falls-short-new-liver-cancer-trial/2014-03-11
[52] http://www.businessweek.com/news/2014-01-21/merck-tobristol-myers-face-more-threats-on-india-drug-patents#p2
[53] This patent has been subject to a compulsory license in India.
[54] The same patent has been opposed in India (1960/DELNP/2007), withdrawn and rejected in South Korea. See. https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2006034797&recNum=1&tab=NationalPhase&maxRec=2&office=&prevFilter=&sortOption=Pub+Date+Desc&queryString=ALL%3A%28PCT%2FEP05%2F010119%29 , See also India patent office database at: http://ipindiaservices.gov.in/publicsearch/
[55] The same patent application remains pending in India (6680/DELNP/2007). See India patent office database: http://ipindiaservices.gov.in/publicsearch

TABLE 5: PRICES OF SORAFENIB IN SOUTH AFRICA AND INDIA

Sorafenib is generally provided as long term treatment, for as long as clinical benefit is provided, at standard dosages of 800mg daily. The cost of a month's treatment in South Africa's private sector is ZAR 26,252 (US$1,856). Generic versions in India are available, thanks to a compulsory license issued in 2012, at 94% lower prices than those charged by Bayer for the originator product in SA. [4]

DOSAGE AND FORMULATION	PRICES OF ORIGINATOR PRODUCT IN SA PRIVATE SECTOR [2]	PRICES OF ORIGINATOR PRODUCT IN SA PUBLIC SECTOR [1]	PRICES OF GENERIC PRODUCTS IN INDIA [11]
200mg +	ZAR 218.76 US$ 15.47	Not procured	ZAR 12.13 US$ 0.86 (Cipla)

+ price per single tablet

TABLE 6: EXAMPLES OF PATENTS GRANTED ON SORAFENIB IN SOUTH AFRICA

PATENT TITLE	PATENT HOLDER	CIPC NUMBER	LODGING DATE:	GRANT DATE	EXPIRY DATE	LEGAL STATUS	PCT NUMBER
CARBOXYARYL SUBSTITUTED DIPHENYL UREAS AS RAF KINASE INHIBITORS	Bayer	2001/05751	12-Jul-2001	23-Sep-2003	12-Jul-2021	Granted	PCT/US000648/00[53]
THERMODYNAMICALLY STABLE FORM OF BAY 43-90006 TOSYLATE	Bayer	2007/02510	27-Mar-2007	0-Jul-2008	27-March-2027	Granted	PCT/EP05/010119[54]
PHARMACEUTICAL COMPOSITION COMPRISING AN AMEGA-CARBOXYARYL SUBSTITUTED DIPHENYL UREA FOR THE TREATMENT OF CANCER	Bayer	2007/07638	05-Sep-2007	26-Aug-2009	5-Sep-2027	Granted	PCT/EP06/001574[55]

See more at: http://www.fixthepatentlaws.org/wp-content/uploads/2014/10/Sorafenib-FINAL.pdf

Photo supplied by the Treatment Action Campaign

HEPATITIS

CASE STUDY 4: ENTECAVIR

For treatment of hepatitis B, entecavir is given daily for life. In South Africa, a month of entecavir costs between ZAR 2,755 (US$ 195) and ZAR 5,510 (US$ 390), depending upon the dosage required. With the removal of patent barriers globally – allowing for greater economies of scale in production – entecavir could be available for as little as ZAR 41 (US$ 3) per month.

What is entecavir used for?

Entecavir is used to treat chronic hepatitis B virus (HBV) and is the treatment of choice for HBV patients with kidney impairment where the use of tenofovir or lamivudine is precluded or not advised. Treatment with entecavir does not cure the infection, but keeps the virus under control – reducing patients' risks of developing many of the complications of HBV infection, like cirrhosis of the liver or liver cancer.[56]

What are the rates of hepatitis B in South Africa?

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.[57] An estimated 3 – 4 million black South Africans have chronic HBV infection.[58] The rates of HBV patients with kidney impairment are unknown, but it is estimated that around 5 – 10% of patients on dialysis are HBV positive.[59]

How available is entecavir in South Africa's public and private healthcare sectors?

Access to entecavir is extremely limited in South Africa's public sector and only available under special circumstances following approval from a hospital Pharmacy Committee. [4] In the private sector, the cost of entecavir is not covered by private insurers for patients with hepatitis B. [9]

How do patents impact on access to entecavir?

In South Africa only Bristol-Myers Squibb's originator product is registered, and sold under the brand name Baraclude. [1.2] Generic versions are already available in India, the US and other countries. [8]

The patent on entecavir's base compound expired in South Africa in 2011, and in other countries between 2011 and 2012.[60] In India, the base compound patent was not filed, but a secondary composition patent was filed on lower dose entecavir.

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[56] 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
[57] 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
[58] http://www.sajei.co.za/index.php/SAJEI/article/view/73
[59] Communication with the Liver Clinic and Division of Hepatology at Groote Schuur Hospital.
[60] ZA1991/07894
[61] The patent in dispute in India involves IN213457, equivalent to WO/2001/64221, and South Africa patent no. ZA 2002/05900. On the court case and settlement, see: "The Entecavir mystery: Natco and BMS enter into a hush-hush patent settlement in India"
[62] http://www.financialexpress.com/article/industry/companies/cipla-bms-settle-hepatitis-b-drug-dispute-out-of-court/86627/
[63] ZA2002/05900, PCT/US01/02630
[64] The patent in dispute in US concerns US5206244 patent concerning composition of entecavir molecule. See: http://www.pmlive.com/pharma_news/teva_wins_challenge_to_bms_baraclude_patent_in_us_463536
[65] http://www.medicines.org.uk/emc/medicine/18377#POSOLOGY
[66] Hill A et al. Analysis of minimum target prices for production of entecavir to treat hepatitis B in high- and low-income countries. Journal of Virus Eradication 01/2015; 1:103-110.
[67] http://bms.newshq.businesswire.com/press-release/financial-news/bristol-myers-squibb-reports-fourth-quarter-and-full-year-2013-financia

TABLE 7: PRICES OF ENTECAVIR PRODUCTS IN SOUTH AFRICA AND INDIA

DOSAGE AND FORMULATION	PRICES OF ORIGINATOR PRODUCTS IN SA PRIVATE SECTOR [2]	PRICES OF ORIGINATOR PRODUCTS IN SA PUBLIC SECTOR [1]	PRICES OF GENERIC PRODUCTS IN INDIA [11]
0.5mg tablet +	ZAR 91.85 US$ 6.50	Not procured	ZAR 16.06 US$ 1.36 (Cipla)
1mg tablet +	ZAR 183.65 US$ 12.99		ZAR 29.98 US$ 2.12 (Cipla)

+ price per single tablet

The secondary composition patent was challenged in India by generic producers Natco and Cipla. The cases were eventually settled out of court, allowing for the sale of generic products in India.[61,62] The same composition patent remains valid in South Africa and could block the use of generic products in the country until 2022.[63]

Generic versions of entecavir are already available in the US after a product patent (filed on modified entecavir composition) was overturned following a legal challenge by generic company Teva.[64]

Bristol-Myers Squibb should clarify that it will not enforce its secondary composition patent in South Africa, to allow people living in South Africa to access lower cost generic products.

Prices of entecavir products in South Africa and India

For treatment of hepatitis, 0.5 to 1mg of entecavir is given daily for life.[65] In South Africa, a month of entecavir costs between ZAR 2,755 (US$ 195) and ZAR 5,510 (US$ 390), depending upon the dosage required. [2] The costs of equivalent generic products in India are approximately ZAR 480 (US$ 34) to ZAR 896 (US$ 63). [4]

A recent study reported that the removal of patent barriers globally could allow for greater economies of scale in production of entecavir, and the medicine could be produced and packaged for as little as ZAR 41 per month – significantly less than the current costs of generic entecavir products[66], at ZAR 480 per month.

What did the patent holder earn during 2013?

During 2013, Bristol-Myers Squibb generated US$ 412 million from the sale of Baraclude globally.[67]

How could reforming South Africa's patent laws improve access to entecavir?

If South Africa reformed its laws to adopt stricter patentability criteria, as well as examination and opposition procedures to ensure that patents were only granted on applications meeting patentability criteria, then it is likely that the secondary patent on entecavir would not have been granted, allowing for the use of generic products in the country.

TABLE 8: PATENTS GRANTED ON ENTECAVIR IN SOUTH AFRICA

PATENT TITLE	PATENT HOLDER	CIPC NUMBER	LODGING DATE:	GRANT DATE	EXPIRY DATE	LEGAL STATUS	PCT NUMBER
HYDROXYMETHYL (METHYLENECYCLOPENTYL) PURINES AND PYRIMIDINES	E.R. Squibb & Sons*	1991/07894	02-Oct-1991	31-Mar-1993	02-Oct-2011	Expired	N/A
LOW DOSE ENTECAVIR FORMULATION AND USE	Bristol-Myers Squibb	2002/05900	23-Jul-2002	26-May-2004	23-Jul-2022	Granted	PCT/US01/02630

* E.R. Squibb & Sons is part of Bristol-Myers Squibb

See more at: http://www.fixthepatentlaws.org/wp-content/uploads/2014/10/Entecavir_Final1LD1.pdf

"Generic entecavir at a fraction of the cost is available outside of South Africa"

By Prof Mark Sonderup, Vice Chairman of the South African Medical Association and clinician in the Liver Clinic and Division of Hepatology at Groote Schuur Hospital.

"Entecavir is an effective drug in the treatment of chronic hepatitis B virus infection. It has been available for almost a decade and long-term efficacy and safety data is now well established. Its counterpart, tenofovir, is equally effective however with several major differences. Tenofovir, used extensively in HIV management, is generically available in South Africa at very affordable prices. It is a very safe and effective therapy for hepatitis B but has some major limitations. Firstly, it has a small but significant risk of causing kidney dysfunction and hence cannot be used in those with existing acute or chronic kidney disease. This creates problems for those who desperately need hepatitis B treatment but in whom tenofovir is contraindicated. The only alternative is to use lamivudine; however, although lamivudine is effective, it lacks the potency and robustness of tenofovir or entecavir and resistance to lamivudine develops over time.

One of my current patients, for instance, who could benefit from entecavir is a 38-year-old HIV-hepatitis B co-infected lady with chronic hepatitis B-associated kidney disease. Ordinarily, joint use of lamivudine- and tenofovir-based ART would be excellent therapy for her hepatitis B, but this cannot be used: she developed lamivudine resistance after three years, with rising hepatitis B levels, and the tenofovir may further damage her kidneys, causing kidney failure. She would then need kidney dialysis to stay alive; however, this is a scarce resource and there is no guarantee she will access this treatment. Furthermore, with uncontrolled hepatitis B, she is not a kidney transplant candidate. Her only hope is to add entecavir to her treatment, but at more than ZAR 4 500 a month for entecavir, this is not accessible to her, or many other patients that could benefit from it. Generic entecavir at a fraction of the cost is available outside of South Africa.

It seems a paradox that a young woman may die with a fully treated and suppressed HIV viral load but untreated hepatitis B. Surely the same principles applying to HIV should apply to hepatitis B in terms of life saving drug access?"

This story was written by Prof Sonderup on 21 December 2015.

PAIN AND EPILEPSY

CASE STUDY 5: PREGABALIN

Private sector purchasers of pregabalin in South Africa could save ZAR 51.8 million (US$ 3.7 million) per year if generic competition was introduced and prices comparable to India could be realized. At lower prices, this medicine could also likely be provided in the public sector.

What is pregabalin used for?

Pregabalin is used to treat fibromyalgia and to relieve neuropathic pain resulting from nerve damage. Pregabalin is also sometimes used to treat certain types of seizures (focal seizures) in people with epilepsy.[68, 69]

What are the rates of fibromyalgia, neuropathic pain and epilepsy in South Africa?

South Africa is estimated to have higher rates of the fibromyalgia than the U.S. and Western Europe.[70, 71] A study of a rural South African community reported that fibromyalgia affects 3.2% of the population.[72,73] Given difficulties in identifying and diagnosing patients with neuropathic pain, limited data is available on prevalence of neuropathic pain in the country.[74,75]

South Africa also has high rates of epilepsy; the disorder affects approximately 1% of people living in the country (versus 0.5% of the global population) [76] – although the rates of focal seizures are unknown.[77]

How available is pregabalin in South Africa's public and private healthcare sectors?

Pregabalin is not procured nationally for use in the public sector. [1] Private insurers are not required to cover the full cost of pregabalin as it is not a prescribed minimum benefit for the treatment of epilepsy, nor is treatment of neuropathic pain fully covered as a prescribed minimum benefit. [9]

How do patents impact on access to pregabalin?

In South Africa, only Pfizer's originator version of pregabalin is available, sold under the brand name Lyrica. Patent protections held by Pfizer could block the use of more affordable generic pregabalin in South Africa until 2022. [2,3] Generic versions of pregabalin are already available in Canada, Russia, India and the UK where the primary patent has expired.[78] Pfizer has been pursuing a patent on what it claims is a "second medical use" of its old drug. So-called new use patent claims are not patentable in a number of countries.[79] In the UK, the initial patent on pregabalin for use in treating epilepsy expired in 2014 and the London High

[68] http://www.cochrane.org/CD010567/SYMPT_antiepileptic-drugs-to-treat-neuropathic-pain-or-fbromyalgia-an-overview-of-cochrane-reviews
[69] http://www.drugs.com/lyrica.html
[70] https://www.researchgate.net/profile/Hueseyin_Guelec/publication/7665422_The_prevalence_of_fibromyalgia_in_women_aged_20-64_in_Turkey/links/0deec5390c7154dfe3000000.pdf
[71] http://www.cdc.gov/arthritis/basics/fibromyalgia.htm
[72] https://www.researchgate.net/profle/Hueseyin_Guelec/publication/7665422_The_prevalence_of_fbromyalgia_in_women_aged_20-64_in_Turkey/links/0deec5390c7154dfe3000000.pdf
[73] http://www.sciencedirect.com/science/article/pii/S1521694203000421
[74] http://www.scielo.org.za/scielo.php?pid=S0256-95742012000500028&script=sci_arttext&tlng=es
[75] www.sapj.co.za/index.php/SAPJ/article/download/2030/3586
[76] http://www.epilepsy.org.za/facts/child.php
[77] Email communication with Epilepsy SA.
[78] The basic patent of pregabalin itself, WO/1993/023383, PCT/US1993/004680, began expiring in 2013. Refer to. https://patentscope.wipo.int/search/en/detail.jsf?docId=WO1993023383&recNum=6&maxRec=6&office=&prevFilter=&sortOption=Pub+Date+Desc&queryString=ALL%3A%28+WO9323383%29&tab=PCT+Biblio
[79] WHO/ICTSD. 2007. 'Guidelines for the Examination of Pharmaceutical Patents: Developing a Public Health Perspective. A Working Paper'. See pgs 21-23. Available at: http://apps.who.int/medicinedocs/documents/s21419en/s21419en.pdf

Court ruled in 2015 that an additional patent granted on second medical uses of the medicine was invalid.[80] The same patent remains valid in South Africa until 2017.[81]

Prices of pregabalin in South Africa, India and Canada:

Pregabalin is generally provided as a lifelong treatment, taken twice daily. A single administration is typically in the range of 150 to 300mg, depending on the individual. The cost of a month of treatment in South Africa's private sector ranges between ZAR 323 (US$ 23) [150mg] and ZAR 646 (US$ 46) [300mg]. The cost of generic equivalents of 150 mg tablets in India and Canada are 70% and 40% lower, respectively.

How much did the patent holder earn in 2013 and what savings could be realised if generic products were available?

Globally, Pfizer generated US$ 4.8 billion from the sale of Lyrica in 2013.[82] During the same year, Pfizer earned more than ZAR 74 million (US$ 5.2 million) on sales of pregabalin as an anti-epileptic medicine in South Africa's private sector. [6] Pregabalin is the second highest driver of expenditure on anti-epileptics [5] and the 38th highest driver of expenditure on medicines in South Africa's private sector. [6] Private sector purchasers of pregabalin in South Africa could save ZAR 51.8 million (US$ 3.7 million) per year if generic competition was introduced and prices comparable to India could be realized.

How could reforming South Africa's patent laws improve access to pregabalin?

If South Africa reformed its laws to adopt stricter patentability criteria, as well as substantive examination and opposition procedures to ensure that patents are only granted on applications meeting patentability criteria, then it is likely that the ongoing patents on pregabalin would not have been granted - allowing for the use of more cost-effective generic products in the country.

TABLE 9: PRICES OF PREGABALIN IN SOUTH AFRICA, INDIA AND CANADA

DOSAGE AND FORMULATION	PRICES OF ORIGINATOR PRODUCTS IN SA PRIVATE SECTOR [2]	PRICES OF ORIGINATOR PRODUCTS IN SA PUBLIC SECTOR [1]	PRICES OF GENERIC PRODUCTS IN INDIA [11]	PRICES OF GENERIC PRODUCTS IN CANADA [12]
25mg tablets +	ZAR 2.87 US$ 0.20	Not procured		
75mg tablets +	ZAR 7.18 US$ 0.51		ZAR 1.77 US$ 0.13 (Cipla, Sun, Lupin, Torrent*)	ZAR 4.45 US$ 0.31 (Mylan, Aurobindo, Apotex, Ranbaxy, Sandoz, Teva*)
150mg tablets +	ZAR 10.77 US$ 0.76		ZAR 3.25 US$ 0.23 (Sun, Lupin, Torrent*)	ZAR 6.14 US$ 0.43 (Mylan, Aurobindo, Apotex, Ranbaxy, Sandoz, Teva*)
300mg tablets +				ZAR 6.14 US$ 0.43 (Mylan, Apotex, Ranbaxy, Sandoz, Teva*)

+ price per single tablet *companies listed provide medicines at or lower than this price

TABLE 10: EXAMPLES OF PATENTS GRANTED ON PREGABALIN IN SOUTH AFRICA

PATENT TITLE	PATENT HOLDER	CIPC NUMBER	LODGING DATE:	GRANT DATE	EXPIRY DATE	LEGAL STATUS	PCT NUMBER
ISOBUTYLGABA AND ITS DERIVATIVES FOR THE TREATMENT OF PAIN	WARNER-LAMBERT COMPANY*	1997/06562	23-Jul-1997	25-Mar-1998	23-Jul-2017	Granted	PCT/US1997/012390[83]
ASYMMETRIC SYNTHESIS OF PREGABALIN	WARNER-LAMBERT COMPANY	2002/05878	23-Jul-2002	23-Sep-2003	23-Jul-2022	Granted	PCT/IB2001/000024

* Warner-Lambert Company was acquired by Pfizer in 2000

[80] The second medical use patent (WO/1998/003167, PCT/US1997/012390) was found invalid by the High Court of London. The decision is available at: http://www.bailii.org/ew/cases/EWHC/Patents/2015/2548.html, See also http://www.fiercepharma.com/legal/u-k-judge-backs-lyrica-generic-scolds-pfizer-for-groundless-threats-to-docs

[81] The equivalent patent in South Africa, ZA 1997/06562, remains granted.

[82] http://www.pmlive.com/top_pharma_list/Top_50_pharmaceutical_products_by_global_sales

[83] The same patent has been invalidated in the UK.

"It's quite upsetting to know that generics are out there but you can't get them"

Bernice Lass is taking pregabalin to treat nerve pain resulting from transverse myelitis – a neurological disorder caused by inflammation of the spinal cord. Her medical aid refuses to fully cover the cost of the treatment, as her condition is not covered under prescribed minimum benefits. Bernice is unable to afford the high cost of pregabalin and has had to seek assistance from her family to pay for her treatment.

Photographer: Mark Napier

"My name is Bernice Lass and I live in Montgomery Park in Johannesburg. I used to be a nurse and now I receive a disability pension.

At the age of thirteen I woke up one morning and I couldn't walk – I couldn't move from my waist down. My mom took me to the GP who put me in hospital. I was diagnosed with transverse myelitis and was told I wouldn't walk again. The first thing I asked was 'can I still be a nurse?' and the doctor said 'no'. I said 'well, I'll show you'. It took about a year to start walking properly again after that – although I did still walk with a limp.

For about thirty years I did quite well and then the condition of my back and neck started to decline. I went to see a neurologist and he told me that I would be in a wheelchair in two years. I explained to the doctor that I had a lot of pain and discomfort and he prescribed Lyrica for me.

Lyrica is a drug that helps with nerve pain. I have to take it at night and in the morning. If I don't take it at night I can't get out of the bed in the morning because my back and legs are just so painful I can't move.

My doctor sent a motivation letter to my medical aid requesting they cover the cost of Lyrica, but my medical aid declined saying that there is not enough research in its use for my condition.

My brother and my son have been helping me pay for Lyrica. I feel embarrassed asking them though – as before I was always independent and had my own money.

It makes me very angry that Lyrica has been patented for so long in South Africa and that people here can't access generics. It's quite upsetting to know that generics are out there but you can't get them. I personally know others with my condition who really need this medicine to deal with their pain but just can't afford it. I don't think it's fair that outside of South Africa this medicine is available at a fraction of its price here."

This story has been edited for length and clarity from a transcript of an interview conducted with Bernice Lass on 9 September 2015.

CASE STUDY 6: CELECOXIB

If celecoxib was available in South Africa at prices equivalent to Canada, the private sector could realise annual savings of approximately ZAR 92 million (US$ 6.5 million). At lower prices, the medicine could also likely be provided in the public sector.

What is celecoxib used for?

Celecoxib is used to treat pain in patients with rheumatoid arthritis and osteoarthritis. A Cochrane Review reported that 51% of rheumatoid arthritis patients treated with celecoxib experienced reduced symptoms at 4 weeks, versus only 29% of patients receiving placebo.[84] A systematic review reported that celecoxib was as effective as other non-steroidal anti-inflammatory drugs in treating rheumatoid and osteoarthritis, and that the drug resulted in fewer gastrointestinal side effects.[85]

What are the rates of rheumatoid arthritis and osteoarthritis in South Africa?

Osteoarthritis is the most common form of arthritis. More than a third of adults over the age of 60 show signs of osteoarthritis on X-ray.[86] In line with rates in developed countries, rheumatoid arthritis affects approximately 1% of people living in South Africa.[87]

How available is celecoxib in South Africa's public and private healthcare sectors?

Celecoxib is not procured nationally for use in the public sector. [1] Private insurers are not required to cover the full cost of celecoxib for private sector users as it exceeds the level of care available in the public sector. [9]

How do patents impact on access to celecoxib?

Only Pfizer's originator product, sold under the brand Celebrex, is available in South Africa. [1,2] The base compound patent on celecoxib expired in South Africa in 2014.[88] However, G.D. Searle (owned by Pfizer) holds a patent on the composition of celecoxib that may continue to block availability of generics in South Africa until 2020.[89]

The composition patent upheld in South Africa[90] has been refused in South Korea and withdrawn from European Patent Office.[91] The same patent was granted in India and Canada but has not prevented manufacture and use of generic products in these countries.[92] Pfizer should clarify that it will not seek to enforce its secondary composition patent in South Africa, allowing for the entry of generic products.

A new use patent for the treatment of cancer with methods and compositions of celecoxib and plumbagin is pending, and if granted, could prolong Pfizer's market monopoly.

84 http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003831/abstract;jsessionid=695AA702F0FC8B96EDB561D4B6663CCD.f02t02
85 http://www.bmj.com/content/325/7365/619?variant=full
86 http://www.sapj.co.za/index.php/SAPJ/article/download/989/1454
87 Ally, MMTM, & Visser, CC. (2010). Rheumatoid arthritis. SA Orthopaedic Journal, 9(1), 18-23. Retrieved February 23, 2016, from http://www.scielo.org.za/scielo.php?script=sci_arttext&pid=S1681-150X2010000100003&lng=en&tlng=en
88 ZA 1994/09418, expired.
89 ZA 2000/02722, PCT/US1999/028411. See: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2000032189&recNum=7&maxRec=7&office=&prevFilter=&sortOption=Pub+Date+Desc&queryString=ALL%3A%28PCT%2FUS1999%2F28411%29&tab=PCT+Biblio
90 2000/02722; PCT/US99/28411.
91 https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2000032189&recNum=7&tab=NationalPhase&maxRec=7&office=&prevFilter=&sortOption=Pub+Date+Desc&queryString=ALL%3A%28PCT%2FUS1999%2F28411%29
92 http://brevets-patents.ic.gc.ca/opic-cipo/cpd/eng/patent/2319201/summary.html#tabs1_5
93 http://www.pfizer.com/news/press-release/press-release-detail/pfizer_reports_fourth_quarter_and_full_year_2013_results_provides_2014_financial_guidance

TABLE 11: PRICES OF CELECOXIB IN SOUTH AFRICA, INDIA AND CANADA

DOSAGE AND FORMULATION	PRICES OF ORIGINATOR PRODUCTS IN SA PRIVATE SECTOR [2]	PRICES OF ORIGINATOR PRODUCTS IN SA PUBLIC SECTOR [1]	PRICES OF GENERIC PRODUCTS IN INDIA [11]	PRICES OF GENERIC PRODUCTS IN CANADA [12]
100mg capsules +	ZAR 4.41 US$ 0.31	Not procured	ZAR 0.91 US$ 0.06 (Ranbaxy, Cipla, Dr Reddy's, Sun, Unichem, Cadila*)	ZAR 1.89 US$ 0.13 (Teva, Sandoz, Ranbaxy, Mylan, Apotex*)
200mg capsules +	ZAR 8.83 US$ 0.62		ZAR 1.71 US$ 0.12 (Ranbaxy, Cipla, Dr Reddy's, Sun, Unichem, Cadila*)	ZAR 3.79 US$ 0.27 (Teva, Sandoz, Ranbaxy, Mylan*)

+ price per single capsule *companies listed market medicines at or lower than this price

Prices of celecoxib in South Africa, India and Canada:

Standard dosages of celecoxib range from 200 to 400mg daily. The cost of a month's treatment in South Africa's private sector range from ZAR 264 (US$ 19) [200mg] to ZAR 530 (US$ 37) [400mg]. [2] The cost of a month's treatment of equivalent generic products in India range between ZAR 51 (US$ 4) and ZAR 103 (US$ 7) [12] – 80% lower than the cost of originator products in South Africa.

How much did the patent holder earn in 2013 and what savings could be realised if generic products were available?

Globally, Pfizer generated US$ 2.9 billion from the sale of Celecoxib in 2013.[93] In the same year, Pfizer earned more than ZAR 160 million (US$ 11.3 million) from the sale of celecoxib in South Africa's private sector. [5] If celecoxib was available in South Africa at prices equivalent to Canada or India, the private sector could have realised savings of approximately ZAR 92 million (US$ 6.5 million) and ZAR 126 million (US$ 8.9 million), respectively.

How could reforming South Africa's patent laws improve access to celecoxib?

If South Africa reformed its laws to adopt stricter patentability criteria, as well as examination and opposition procedures to ensure that patents were only granted on applications meeting patentability criteria, then it is likely that the current patent on celecoxib would not have been granted. Stricter patentability criteria and substantive examination could also help rule out the pending application on a new use of celecoxib.

TABLE 12: EXAMPLES OF PATENTS GRANTED ON CELECOXIB IN SOUTH AFRICA

PATENT TITLE	PATENT HOLDER	CIPC NUMBER	LODGING DATE	GRANT DATE	EXPIRY DATE	LEGAL STATUS	PCT NUMBER
SUBSTITUTED PYRAZOLYL BENZENESULFONAMIDES FOR THE TREATMENT OF INFLAMMATION	GD Searle & Co*	1994/09418	28-Nov-1994	28-Nov-1995	28-Nov-1994	Expired	N/A
CELECOXIB COMPOSITIONS	GD Searle & Co*	2000/02722	31-May-2000	31-Jan-2001	May 2020	Granted	PCT/US99/28411
COMPOSITIONS AND METHODS INCLUDING CELECOXIB AND PLUMBAGIN RELATING TO TREATMENT OF CANCER	The Penn State Research Foundation	2015/06392	1-Sept-2015			Pending	PCT/US2013/032439

* G.D. Searle is owned by Pfizer

MENTAL HEALTH

CASE STUDY 7: ARIPIPRAZOLE

The cost of a month of treatment in South Africa's private sector ranges between ZAR 1,090 (US$ 77) to ZAR 2,408 (US$ 170), depending on the dosage required. The cost of a month of generic equivalents in India range between ZAR 37 (US$ 3) to ZAR 89 (US$ 6).

What is aripiprazole used for?

Aripiprazole is an anti-psychotic medication used for the treatment of schizophrenia, bipolar disorder, major depressive disorder and autistic disorders.[94] Aripiprazole is more tolerable for patients and has fewer side-effects than typical anti-psychotic drugs.[95]

What are the rates of schizophrenia, bipolar disorder and major depression disorder in South Africa?

Approximately 1% – 2% of the world's population is afflicted by these illnesses; onset is usually between the ages of 15 and 30. Around one-third of the South African population (about 17.6 million people) will suffer from a mental disorder at some point in their lifetime; this includes major depression, bipolar disorder, schizophrenia, or anxiety and substance abuse.[96]

How available is aripiprazole in South Africa's public and private healthcare sectors?

Aripiprazole is not procured nationally for use in South Africa's public sector [1] and only limited access is available under certain, specific circumstances. [10] Aripiprazole is only fully covered as a prescribed minimum benefit by private insurers if patients have previously failed on other first-line anti-psychotic treatments. [9]

How do patents and regulatory barriers impact on access to aripiprazole?

Only Bristol-Myers Squibb's originator version of aripiprazole, marketed under the brand name Abilify is available in South Africa. [1,2] The patent on the base compound of aripiprazole was filed around 1988-1989[97] by Japanese company Otsuka, and expired in most countries between 2014 and 2015 (extensions and evergreening patents extended the life of this patent beyond 20 years[98]). Otsuka has a marketing agreement for aripipiprazole with Bristol-Myers Squibb covering the South African market.

Multiple generic companies are already supplying other countries' markets, including at least eight generic producers approved in the US market alone.[99]

In South Africa the base patent on aripiprazole has expired, which should allow for use of generic products. Yet, Otsuka has sought and received multiple secondary patents on aripiprazole in South Africa, creating complexity and uncertainty regarding the patent status of this medicine. Generic producers of aripiprazole further indicated regulatory delays as a disincentive and barrier to the introduction of generic aripiprazole to the market.[100]

Otsuka and Bristol-Myers Squibb should clarify that they will not seek to enforce secondary patents in South Africa, allowing for the use of generic products.

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[94] http://www.nlm.nih.gov/medlineplus/druginfo/meds/a603012.html
[95] http://www.cochrane.org/CD006617/SCHIZ_aripiprazole-versus-typical-antipsychotic-drugs-for-schizophrenia
[96] http://africacheck.org/reports/do-a-third-of-south-africans-really-sufferfrom-mental-illnesses/
[97] EP0367141, http://worldwide.espacenet.com/publicationDetails/originalDocument;jsessionid=Nub3ue7LMbO0n5YzEnFdsVtL.espacenet_levelx_prod_3?FT=D&date=19900509&DB=&locale=en_EP&CC=EP&NR=0367141A2&KC=A2&ND=1
[98] The patent should have expired in Europe in 2009, but was extended until 2015 through a Supplementary Protection Certificate. In the US, an evergreening patent granted on a paediatric formulation extended the life of this patent until 2014.
[99] US FDA Orange Book register: http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm
[100] Email communication with generic producers of aripiprazole during April 2016.
[101] http://www.fiercepharma.com/special-reports/abilify-best-selling-drugs-2013

TABLE 13: PRICES OF ARIPIPRAZOLE IN SOUTH AFRICA AND INDIA

DOSAGE AND FORMULATION	PRICES OF ORIGINATOR PRODUCTS IN SA PRIVATE SECTOR [2]	PRICES OF ORIGINATOR PRODUCTS IN SA PUBLIC SECTOR [1]	PRICES OF GENERIC PRODUCTS IN INDIA [11]
5mg tablet +	ZAR 25.70 US$ 1.82	Not procured	
10mg tablet +	ZAR 36.32 US$ 2.56		ZAR 1.24 US$ 0.09 (Nicolas Piramal)
15mg tablet +	ZAR 48.84 US$ 3.45		ZAR 1.75 US$ 0.12 (Nicolas Piramal)
30 mg tablet +	ZAR 80.27 US$ 5.68		ZAR 2.98 US$ 0.21 (Nicolas Piramal)
7.5mg/ml injection (1.3ml) ++	ZAR 80.85 US$ 5.72		

+ price per single tablet

++ price per single ml

Prices of aripiprazole in South Africa and India:

Aripiprazole is generally provided as a lifelong treatment at 10 to 30mg per day. The cost of a month of treatment in South Africa's private sector ranges between ZAR 1,090 (US$ 77) [10mg] to ZAR 2,408 (US$ 170) [30mg]. The cost of a month of generic equivalents in India ranges between ZAR 37 ($3) [10mg] to ZAR 89 (US$ 6) [30mg].

How much did the patent holder earn in 2013?

Globally Bristol-Myers Squibb and Otsuka jointly generated US$5.5 billion from the sale of Abilify during 2013.[101] In the same year, Bristol-Myers Squibb earned over ZAR 30 million (US$ 2.1 million) in annual revenue from the sale of aripiprazole in South Africa's private sector. [5] If South Africa had access to generic products at Indian prices, over ZAR 29 million (US$ 2 million) in savings annually could be realized on this medicine by private sector users and medical aids if private sector users selected generic products. [4]

How could reforming South Africa's patent laws improve access to apripirazole?

If South Africa reformed its laws to adopt stricter patentability criteria, as well as examination and opposition procedures to ensure that patents were only granted on applications meeting patentability criteria, then it is likely that the ongoing patents on aripiprazole would not have been granted.

Photographer: Ton Koene

TABLE 15: PATENTS GRANTED ON ARIPIPRAZOLE IN SOUTH AFRICA

PATENT TITLE	PATENT HOLDER	CIPC NUMBER	LODGING DATE:	GRANT DATE	EXPIRY DATE	LEGAL STATUS	PCT NUMBER
ARIPIPRAZOLE ORAL SOLUTION	OTSUKA PHARMACEUTICAL*	2003/07797	06-Oct-2003	29-Dec-2004	26-Oct-2023	Granted	PCT/US02/013048
LOW HYGROSCOPIC ARIPIPRAZOLE DRUG SUBSTANCE AND PROCESSES FOR THE PREPARATION THEREOF	OTSUKA PHARMACEUTICAL	2003/00113	06-Jan-2003	27-Oct-2004	06-Jan-2023	Granted	PCT/ JP2002/09858
CONTROLLED RELEASE STERILE INJECTABLE ARIPIPRAZOLE FORMULATION AND METHOD	OTSUKA PHARMACEUTICAL	2006/02347	28-Mar-2006	26-Sep-2007	28-March -2026	Granted	PCT/US04/034367
METHODS FOR PRODUCING ARIPIPRAZOLE SUSPENSION AND FREEZE-DRIED FORMULATION	OTSUKA PHARMACEUTICAL	2010/00307	15-Jan-2010	28-Apr-2011	15-Jan-2030	Granted	PCT/JP08/064076
MEDICAL DEVICE CONTAINING A CAKE COMPOSITION COMPRISING ARIPIPRAZOLE AS AN ACTIVE INGREDIENT, AND A CAKE COMPOSITION ARIPIPRAZOLE AS AN ACTIVE INGREDIENT	OTSUKA PHARMACEUTICAL	2013/05199	10-Jul-2013	25-Sep-2014	10-Jul-2033	Granted	PCT/JP12/051285
DUAL CHAMBER PREFILLABLE SYRINGE AND ARIPIPRAZOLE FILLED IN SYRINGE	OTSUKA PHARMACEUTICAL	2013/03514	14-May-2013	N/A	14-May-2033	Accepted	PCT/JP11/076385
FREEZE-DRIED ARIPIPRAZOLE FORMULA TION	OTSUKA PHARMACEUTICAL	2013/08868	19-Nov-2013	25-Feb-2015	19-Nov-2033	Granted	PCT/JP12/065180
METHOD FOR PRODUCING FINE PARTICLES OF ARIPIPRAZOLE ANHYDRIDE	OTSUKA PHARMACEUTICAL	2013/09246	09-Dec-2013	29-Apr-2015	09-Dec-2033	Granted	PCT/JP12/067258

* Otsuka Pharmaceuticals have a marketing agreement with Bristol-Myers Squibb who market aripiprazole in South Africa

"I haven't done anything wrong, I am an ill person, accessing medications and I am absolutely punished for doing so"

Amy has battled with mental illness from an early age. She suffers from bipolar disorder, epilepsy, PTSD and ADHD. Among other medications, she takes the anti-psychotic drug aripiprazole – sold under the brand name Abilify.*

Photographer: Mark Napier

"I saw my first psychiatrist when I was 13 years old. In 2010, I was diagnosed with Type 2 bipolar disorder. My doctor recommended that I start taking Abilify. After a few weeks of treatment, I noticed a huge difference in my functioning.

My psychiatrist had provided a strong motivation to my medical aid that it was vital for me. The medical aid said they didn't cover the drug in their formulary but that they'd pay a nominal amount towards it.

As my bipolar fluctuated the dosage was increased. Out of the blue, my medical aid announced they were dropping my cover. It was a shock because every month I put together a budget and I know I've got X amount to spend on my healthcare, X amount on transport, on rent and so on.

Abilify costs ZAR 1,376 (at 15mg daily per month) and my medical aid only covers ZAR 550 of its total cost. My monthly co-payment is nearly ZAR 2,000 for all my meds. That is an obscene amount of money to be spending on health care. I haven't done anything wrong, I am an ill person, accessing medications and I am absolutely punished for doing so.

I believe years and years of progress in controlling and managing my illness would be lost if I were to lose my job tomorrow and be unable to access aripiprazole. This is really problematic because I wouldn't be able to get Abilify through the state.

I have been hospitalised in the past for a bipolar episode. It's not an easy process. If I couldn't access Abilify, going back into hospital would be inevitable."

This story has been edited for length and clarity from the transcript of the interview conducted with Amy on 13 September 2015.

**At her request, Amy has been provided with a pseudonym to protect her anonymity.*

SEXUAL AND REPRODUCTIVE HEALTH

CASE STUDY 8: DROSPIRENONE AND ETHINYL ESTRADIOL

> The same secondary patent being upheld in South Africa has been revoked by courts in Europe and the USA.

What is drospirenone and ethinyl estradiol used for?

Drospirenone and ethinyl estradiol is a combination oral contraceptive for use by women to prevent pregnancy. Drospirenone and ethinyl estradiol is also registered as a treatment for premenstrual dysphoric disorder (PMDD) and for moderate acne in women who are using the pill for birth control.[102]

How many women use drospirenone and ethinyl estradiol in South Africa?

Approximately 141,000 women in South Africa use drospirenone and ethinyl estradiol – procured via private facilities and pharmacies.

How available is drospirenone and ethinyl estradiol in South Africa's public and private healthcare sectors?

Drospirenone and ethinyl estradiol is not available to patients using South Africa's public sector. [1] Private insurers are not required to fully cover the costs of drospirenone and ethinyl estradiol in the private sector as it exceeds the level of care provided in the public sector. [9]

How do patents impact on access to drospirenone and ethinyl estradiol?

In South Africa, only Bayer's originator versions of this medicine are available, sold under the brand names Yasmin and Yaz. [1,2] In 2011, Pharma Dynamics registered a generic version of Yasmin for sale in South Africa after the initial patent on the medicine expired in 2010.[103] To prevent Pharma Dynamics from marketing its generic product, Bayer brought a legal challenge against Pharma Dynamics for infringement of Bayer's additional, unexpired patents held on the medicine.

South Africa's Supreme Court of Appeal determined that Pharma Dynamics' product infringed upon an ongoing divisional patent[104], granted on the original patent which had already expired.[105] The court ruling upholding Bayer's secondary patents will block the sale of generic drospirenone and ethinyl estradiol in South Africa until 2024.[106] The patent under dispute concerned the so called 'divisional applications' that represent part of the claims contained in an original application.[107] As each divisional application could be misused in prolonging the uncertainty for competitors, it has been recommended that countries limit the granting of these types of patents through rigorous patent examination.[108] [3,4]

The same secondary patent being upheld in South Africa has been revoked by courts in Europe[109] and the USA,[110] where generic

[102] Yasmin® [package insert]. Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ; April 2012. http://labeling.bayerhealthcare.com/html/products/pi/fhc/Yasmin_PI.pdf?WT.mc_id=www.berlex.com. Accessed July 23, 2014.
[103] http://www.fixthepatentlaws.org/wp-content/uploads/2014/10/YasminFinal_3.pdf
[104] The divisional patent in dispute concerns ZA2004/04083.
[105] The original patent ZA1990/03754 expired in South Africa in 2010.
[106] The divisional patents concerned in the case are ZA2002/01668 and ZA2004/04083, in corresponding to WO/2001/015701,PCT/IB2000/001213. The same patents have also been refused in South Korea. See: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2001015701&recNum=1&maxRec=&office=&prevFilter=&sortOption=&queryString=&tab=PCT+Biblio
[107] Correa C. 'Tackling the Proliferation of Patents'. South Centre 2015. p 20. Available at: http://www.southcentre.int/wp-content/uploads/2014/09/RP52_Tackling-the-Proliferation-of-Patents-rev_EN.pdf
[108] Ibid. Page 23.
[109] EP1214076, See legal status as 'patent revoked' at: https://register.epo.org/application?number=EP00953387109; http://www.law360.com/articles/115159/fed-circ-affrms-invalidity-of-bayer-s-yasmin-patent, See also: http://www.fxthepatentlaws.org/wp-content/uploads/2014/10/YasminFinal_3.pdf
[110] http://www.fixthepatentlaws.org/wp-content/uploads/2014/10/YasminFinal_3.pdf
[111] http://www.fixthepatentlaws.org/wp-content/uploads/2014/10/YasminFinal_3.pdf
[112] http://www.annualreport2013.bayer.com/en/bayer-annual-report-augmented-version-2013.pdfx

TABLE 15: PRICES OF DROSPIRENONE AND ETHINYL ESTRADIOL IN SOUTH AFRICA

DOSAGE AND FORMULATION	PRICES OF ORIGINATOR PRODUCTS IN SA'S PRIVATE SECTOR [2]	PRICES OF ORIGINATOR PRODUCTS IN SA PUBLIC SECTOR [1]	PRICE OF GENERIC PRODUCT BLOCKED FROM SALE IN SA[110]
3mg/0.3mg tablet (Yasmin) +	ZAR 4.44 US$ 0.31	Not procured	ZAR 2.89 US$ 0.20 (Pharma Dynamics)
3mg/20mcg tablet (Yaz) +	ZAR 5.37 US$ 0.38		

+ price per single tablet

versions of drospirenone and ethinyl estradiol have already been available for several years.[111]

Prices of drospirenone and ethinyl estradiol in South Africa:

In 2011 Pharma Dynamics sought to introduce their generic product at a 30% lower price than that charged by Bayer for its originator products – although Bayer's secondary patents upheld by the Supreme Court of Appeal blocked Pharma Dynamics from marketing its more affordable generic product in the country.

How much did the patent holder earn in 2013 and what savings could be realised if generic products were available?

During 2013, Bayer earned US$934 million from the sale of Yasmin and Yaz globally.[112] In the same year, Bayer earned more than ZAR 170 million (US$ 12 million) from the sale of Yasmin and Yaz in South Africa's private sector. [5] If Pharma Dynamics' generic product was available in South Africa, women using the private sector would have the option to save approximately ZAR 50 million (US$ 3.5 million) collectively per year through generic substitution.

How could reforming South Africa's patent laws improve access to drospirenone and ethinyl estradiol?

South Africa could set stricter patentability criteria to ensure that patents are only granted on applications where legitimate innovation is demonstrated. Patentability criteria could put limits on granting divisional patent applications, meaning patents like the one on Yasmin would not be upheld in court. If secondary patents had been overturned on Yasmin by the Supreme Court of Appeal, then generic products would already be available in the country.

TABLE 18: PATENTS GRANTED ON DROSPIRENONE AND ETHINYL ESTRADIOL IN SOUTH AFRICA

PATENT TITLE	PATENT HOLDER	CIPC NUMBER	LODGING DATE: COMPLETE	GRANT DATE	EXPIRY DATE (20 YEARS AFTER LODGING DATE)	LEGAL STATUS	PCT NUMBER
DIHYDROSPIRORENONE AS AN ANTIANDROGEN	SCHERING AKTIENGE-SELLSCHAFT*	1990/03754	16-May-1990	27-Feb-1991	16-May-2010	Granted/ Expired	N/A
PHARMACEUTICAL COMBINATION OF ETHINYLESTRADIOL AND DROSPIRENONE FOR USE AS A CONTRACEPTIVE	SCHERING AKTIENGE-SELLSCHAFT*	2002/01668	27-Feb-2002	25-Aug-2004	27-Feb-2022	Granted	PCT/ IB2000/ 001213
		2004/04083	25-May-2004	22-Feb-2006	25-May-2024	Granted	

*Schering AG was bought by Bayer in 2006, forming Bayer Schering Pharma AG

HIV

CASE STUDY 9: LOPINAVIR/RITONAVIR

During 2015, widespread stock outs and treatment interruptions resulted from the patent holder's inability to deliver adequate supply of LPV/r - a drug taken by hundreds of thousands of people receiving HIV treatment in the public sector.

What is LPV/r used for?

Lopinavir/ritonavir (LPV/r) is a combination antiretroviral (ARV) medicine, used in standard first-line ARV regimens for paediatric patients with HIV, and second-line regimens for adults and adolescents with HIV who have developed resistance to first-line treatments.

How big is the need for LPV/r in South Africa?

An estimated 160,000 people in South Africa were taking LPV/r in November 2015[113], with numbers certain to increase as South Africa moves to a "Test and Start" policy for all people living with HIV.[114]

How available is LPV/r in South Africa's public and private healthcare sectors?

LPV/r is tendered nationally for public sector use at primary care levels. [1] LPV/r is a prescribed minimum benefit, requiring private insurers to cover its full cost for their members. [9] Currently, manufacturer AbbVie dominates the public and private sectors as the only supplier of LPV/r - marketed under the brand name Aluvia. [1.2]

How have patents impacted on access to LPV/r?

During 2015, severe shortages of LPV/r across South Africa resulted from AbbVie's inability to deliver adequate supply and led to treatment interruptions for patients.[115] In a national survey of public health facilities carried out between October to December 2015, LPV/r formulations made up over 37% of all 767 ARV or TB medicine stock-outs reported.[116]

Multiple patents held by AbbVie run until 2026 in South Africa, including on both single dose molecule ritonavir and combinations of lopinavir and ritonavir.[117] These patents blocked the use of locally registered and World Health Organisation pre-qualified generic LPV/r products during 2015 supply shortages.

Treatment interruptions resulting from stock-outs place people living with HIV at risk of developing drug resistance and immunological failure. Adults and adolescents who develop resistance to second-line treatment must be switched to third-line treatment – which is the last option of ARV treatment in South Africa's public sector and six times more expensive than the cost of second-line regimens.[118]

Push back from civil society and government:

Stock-outs of LPV/r led to a significant public outcry by civil society during 2015 and calls for the South African government to issue a compulsory license to allow the use of registered generic products. In response to mounting pressure from civil society and the South African government, AbbVie signed a new voluntary license agreement with the Medicines Patent Pool (MPP) in December 2015. This new license covers the adult formulation of LPV/r, and allows eligible and interested generic producers to market their versions in all African countries. A previous license covers two paediatric formulations of LPV/r, though another important paediatric formulation is not included, and remains out of reach.

[113] Kew J. 2015. South Africa asked to allow generics for AbbVie HIV drug. Bloomberg. Available at: http://www.bloomberg.com/news/articles/2015-11-02/south-africa-asked-to-allow-generic-versions-of-abbvie-hiv-drug
[114] Khan T. 10 May 2016. SA to adopt WHO's 'test and treat' HIV guidelines. Business Day. Available at: http://www.bdlive.co.za/national/health/2016/05/10/SA-to-adopt-WHO%E2%80%99s-%E2%80%98test-and-treat%E2%80%99-HIV-guidelines
[115] http://www.msfaccess.org/about-us/media-room/press-releases/south-africa-should-override-patent-key-hiv-medicine-after
[116] http://stockouts.org/uploads/3/3/1/1/3311088/survey_stop_stock_outs_2015.pdf
[117] Information of the patent status of LPV/r in South Africa is available at: http://www.medicinespatentpool.org/table/
[118] http://www.nspreview.org/2015/06/10/weak-rand-means-south-africa-pays-more-for-arvs-in-latest-tender/

As of July 2016, Chinese company Desano and Indian companies Emcure and Aurobindo have signed the sub-licenses for adult formulations of LPV/r, while Indian producer Hetero remains the only company who has taken up the paediatric license on LPV/r.

How could reforming SA's patent laws improve access to LPV/r?

More efficient procedures for granting compulsory licenses would have allowed the South African government to respond more quickly to access generic manufacturers' supply of LPV/r and resolve stock-outs. Supply security will also be extremely important during the scale-up of the "Test and Start" policy for HIV treatment. Full use of TRIPS flexibilities would facilitate sourcing ARVs and their active ingredients from multiple suppliers.

TABLE 17: PATENTS HELD ON LPV/R IN SOUTH AFRICA

PATENT TITLE	PATENT HOLDER	CIPC NUMBER	LODGING DATE	GRANT DATE	EXPIRY DATE:	LEGAL STATUS	PCT/US NUMBER
RETROVIRAL PROTEASE INHIBITING COMPOUNDS	ABBVIE BAHAMAS LTD*	1996/10475	12-Dec-1996	29-Oct-1997	12-Dec-2016	Granted	PCT/US1996/020440
PHARMACEUTICAL COMPOSITION	ABBOTT LABORATORIES	1997/10071	07-Nov-1997	29-Jul-1998	7-Nov-2017	Granted	PCT/US1997/020794
SOLID PHARMACEUTICAL DOSAGE FORM	ABBOTT LABORATORIES	2006/01718	27-Feb-2006		27-Feb-2026	Pending	PCT/US04/027401
A SOLID PHARMACEUTICAL DOSAGE FORMULATION	ABBOTT LABORATORIES	2007/07022	21-Aug-2007	26-Aug-2009	21-Aug-2027	Granted	PCT/US06/005944
SOLID PHARMACEUTICAL DOSAGE FORM	ABBOTT LABORATORIES	2008/01362	08-Feb-2008	25-Mar-2009	8-Feb-2028	Granted	US8691878

*AbbVie is part of Abbott Laboratories, renamed AbbVie in 2013

Photographer: Mariska van den Brink

“Now we’re going back to the beginning where people were dying because of HIV with no access to treatment”

Thandi Shabangu was diagnosed with HIV in 2004. She initiated a second-line antiretroviral treatment regimen after her treatment was interrupted during a period of hospitalisation for meningitis in 2006. Thandi has been able to manage her illness with second-line treatment, until a recent stock-out of lopinavir/ritonavir put her health and life at risk.

Photographer: Mark Napier

“My name is Thandi Shabangu. I live at Tembisa Madimole Section in Gauteng. I am a community worker and I was diagnosed with HIV in 2004.

After I started ARVs, I got meningitis and when I was at the hospital I got so ill I lost track and didn’t take my ARVs. After they discharged me and I started my ARV regimen again, I went for tests and my viral load was too high, and my CD4 count was low. Because I didn’t take my pills for three weeks, I had developed resistance. I started a new second-line regimen which includes Aluvia.

I’m no longer taking Aluvia because of the stock-out. This problem is very big. It’s a matter of life and death for me. If you don’t take your Aluvia, you are going to resist. When my Aluvia was finished I went to the clinic and they told me: ‘No, we don’t have Aluvia. You’re supposed to go to the chemist to buy the Aluvia.’ The challenge is what if people don’t have money or parents or someone to help them get the medicine? I had that problem.

When I went to the clinic, they told me they don’t have adult Aluvia, but they do have children’s Aluvia. I begged

that they must give me children's medication because I can't live without my medication. So now I'm taking the children's pills. We have lots of children living with HIV so if we are taking the pills meant for them… it's a problem because they won't get their pills.

I know if you don't take your pills, you will get sick. Now I am very sick. I'm in pain even now so I don't know what I'm going to do because I have my kids who depend on me. So if now my pills are finished, I don't know what to do because I don't have money, I'm no longer working.
I don't know exactly why there's a stock-out. When you go to the clinic and ask the sisters what the problem is and they tell us that they don't know. I heard that the problem is a patent thing, I heard that we have this one company who supplies Aluvia all over.

You can't depend on only one company to supply you with medicine. We have to have another option because if they stick to one company, it's a problem for us and not for them. It affects us, it affects the community because now we're going back to the beginning where people were dying because of HIV with no access to treatment."

This story has been edited for length and clarity from the transcript of interview conducted with Thandi on 5 October 2015.

Photographer: Mariella Furrer

Spotlight on DR-TB drugs

Photographer: Jose Cendon

BEDAQUILINE, DELAMINID AND LINEZOLID

South Africa has one of the highest global burdens of drug-resistant tuberculosis (DR-TB), with over 18,000 cases diagnosed in 2014.[119] With new drugs for DR-TB becoming available for the first time in over 50 years, reforming the patent laws will be vital for the future of DR-TB treatment in South Africa.

Pharmaceutical company Janssen manufactures bedaquiline (BDQ), which was registered in South Africa in late 2014. Over 1,100 DR-TB patients received BDQ through South Africa's national TB programme in 2015. The government target is to initiate at least 3,000 DR-TB patients on regimens containing BDQ in 2016.

Otsuka, which manufactures delamanid (DLM), has regulatory approval for the drug in Europe, Japan, South Korea and the United Kingdom, but has yet to file for registration in South Africa or most other high-burden DR-TB countries.[120] This means that access to DLM is restricted to only a few patients in South Africa, where clinicians have secured special permission to import the drug. Doctors Without Borders (MSF) in Khayelitsha, Western Cape, have initiated more than 36 patients on regimens containing DLM as of September 2016, and a few other health facilities across the country have a small number of patients taking the drug. If DLM was registered and more widely available, the National Department of Health could introduce it into treatment guidelines in South Africa, and an estimated 7,000 DR-TB patients per year in the country could benefit from the inclusion of DLM in their treatment regimens[121], if World Health Organisation guidance was applied in full.[122]

Patent monopolies and minimal competition can limit the South African government's ability to purchase DR-TB treatments and make them publicly available. For several years, many DR-TB patients were unable to benefit from the drug linezolid while it was under patent, and priced at over ZAR 700 (US$ 49) per 600mg tablet.[123] The patent expired on linezolid in August 2014, with one generic company subsequently entering the South African market. Linezolid was only made avalable through the public sector when tender prices fell to ZAR 100 (US$ 7) per 600mg tablet in March 2016 – though prices could fall further if additional generic competitors are registered.[124]

Both BDQ and DLM are already patented multiple times in South Africa – the latest secondary patent on bedaquiline expires in 2027, on delamanid in 2032 – which could present several challenges to access.[125,126] Chief among these are that Otsuka has not filed for registration of DLM in South Africa, even though the country was the site of clinical trials for DLM, and the finished product has been available in other parts of the globe for several years. This behaviour could be classified as abuse of patent rights, making DLM potentially eligible for a compulsory license to improve access, based on South Africa's laws. (See patent table on page 50).

As DR-TB patients must take multiple drugs as part of a treatment regimen, the combined costs of using multiple new drugs with other treatments – even at the lowest prices offered by patent-holding companies – could rapidly become difficult for the government or patients to afford. The lowest price Janssen has announced for BDQ in any country is US$ 900 (ZAR 12,726) for the six-month treatment course. Otsuka announced its lowest global price for a six-month treatment course in February 2016, at a shockingly high US$1,700 (ZAR 24,038).[127,128] A recent study that developed target price ranges for MDR-TB drugs, based on estimated costs of generic manufacture and a reasonable profit margin, calculated that the target prices for BDQ and DLM treatment courses should be in the range of US$ 50 to US$ 98 and US$ 21 to US$ 52, respectively – more than 90% lower than current offerings.[129]

It will also be important to conduct research on new treatment combinations for DR-TB, to develop shorter, more effective regimens with fewer side effects. Some of the patents granted in South Africa on BDQ and DLM cover their use in combination with other TB drugs, or for treating TB. This could limit the ability of researchers or generic manufacturers to develop better DR-TB treatment combinations if they are not granted permission by the originator companies.

In the immediate term, it is crucial for BDQ and DLM to be made available in South Africa at affordable prices by the originator manufacturers. However, it will be imperative to address patent barriers to lower prices and scale up access to treatment, as was the case with ARVs for HIV in the early 2000s. Potential strategies to consider include the use of compulsory licenses on DLM to address Otsuka's abuse of its patent rights in South Africa; and voluntary licenses or non-enforcement of patent rights by originators, to allow generic companies to start manufacturing and supplying DR-TB drugs like BDQ and DLM at lower prices, and conducting research with new DR-TB drugs.

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[124] http://www.tbonline.info/posts/2016/1/8/urgent-need-make-linezolid-available-south-africa-/
[125] SYNTHETIC INTERMEDIATE OF OXAZOLE COMPOUND AND METHOD FOR PRODUCING THE SAME. Patent 2012/04802. 27 June 2012. Print.
[126] PROCESS FOR PREPARING (ALPHA S, BETA R)-6-BROMO-ALPHA-[2-(DIMETHYLAMINO)ETHYL]-2-METHOXY-ALPHA-1-NAPHTHALENYL-BETA-PHENYL-3-QUINOLINEETHANOL. Patent 2007/10150. 26 Nov. 2007. Print.
[127] http://www.msfaccess.org/about-us/media-room/press-releases/developing-countries-hit-high-price-important-new-tuberculosis-dr
[128] ZAR prices calculated on an exchange rate of $1 = ZAR 14.14.
[129] Gotham D et al. Target generic prices for novel treatments for drug-resistant tuberculosis.15th European AIDS Conference, Barcelona, ab-stract PS2/4, 2015.

TABLE 18: EXAMPLES OF PATENTS GRANTED ON DELAMINID IN SOUTH AFRICA

PATENT TITLE	PATENT HOLDER	CIPC NUMBER	LODGING DATE:	GRANT DATE	EXPIRY DATE:	LEGAL STATUS	PCT/US NUMBER
2,3-DIHYDRO-6-NITROIMIDAZO [2,1-B] OXAZOLES	Otsuka Pharmaceutical Co., Ltd	2005/01033	03-Feb-2005	28-Jun-2006	03-Feb-2025	Granted	PCT/JP03/013070
METHOD OF PRODUCING AMINOPHENOL COMPOUNDS	Otsuka Pharmaceutical Co., Ltd	2006/07640	12-Sep-2006	28-May-2008	12-Sept-2006	Granted	PCT/JP05/006408
PHARMACEUTICAL COMPOSITION COMPRISING 2,3-DIHYDRO-6-NITROIMIDAZO [2,1-B] OXAZOLE DERIVATIVES	Otsuka Pharmaceutical Co., Ltd	2007/10404	30-Nov-2007	29-Oct-2008	30-Nov-2027	Granted	PCT/JP06/314708
ANTITUBERCULOUS COMPOSITION COMPRISING OXAZOLE COMPOUNDS	Otsuka Pharmaceutical Co., Ltd	2008/02883	02-Apr-2008	30-Sep-2009	02-Apr-2028	Granted	PCT/JP06/320239
SYNTHETIC INTERMEDIATE OF OXAZOLE COMPOUND AND METHOD FOR PRODUCING THE SAME	Otsuka Pharmaceutical Co., Ltd	2012/04802	27-June-2012	25-Sep-2013	27-June-2032	Granted	PCT/JP11/052307

TABLE 19: EXAMPLES OF PATENTS GRANTED ON BEDAQUILINE IN SOUTH AFRICA

PATENT TITLE	PATENT HOLDER	CIPC NUMBER	LODGING DATE:	GRANT DATE	EXPIRY DATE:	LEGAL STATUS	PCT/US NUMBER
QUINOLINE DERIVATIVES AND THEIR USE AS MYCOBACTERIAL INHIBITORS	Janssen Pharmaceutica N.V.	2005/00680	24-Jan-2005	30-Aug-2006	24-Jan-2025	Granted	PCT/EP03/050322
USE OF SUBSTITUTED QUINOLINE DERIVATIVES FOR THE TREATMENT OF DRUG RESISTANT MYCOBACTERIAL DISEASES	Janssen Pharmaceutica N.V.	2006/09899	27-Nov-2006	28-Jan-2009	27-Nov-2027	Granted	PCT/EP2005/052371
QUINOLINE DERIVATIVES FOR THE TREATMENT OF LATENT TUBERCULOSIS	Janssen Pharmaceutica N.V.	2007/05160	22-Jun-2007	25-Sep-2008	22-Jun-2027	Granted	PCT/EP05/056594
PROCESS FOR PREPARING (ALPHA S,BETA R)-6-BROMO-ALPHA-[2-(DIMETHYLAMINO) ETHYL]-2-METHOXY-ALPHA-1-NAPHTALENYL-BETA-PHENYL-3-QUINOLINEETHANOL	Janssen Pharmaceutica N.V.	2007/10150	26-Nov-2007	27-Jun-2012	26-Nov-2027	Granted	PCT/EP06/062502
FUMARATE SALT OF (ALPHA S,BETA R)-6-BROMO-ALPHA-[2-(DIMETHYLAMINO) ETHYL]-2-METHOXY-ALPHA-1-NAPHTHALENYL-BETA-PHENYL-3-QUINOLINEETHANOL	Janssen Pharmaceutica N.V.	2009/03907	04-Jun-2009	28-Aug-2013	04-Jun-2029	Granted	PCT/EP07/063186

"The side effects of MDR-TB drugs are a nightmare."

When Phumeza Tisile (23) took the last dose of her tablets she put an end to the daily ritual of the last two years of her life. She took close to 20,000 pills to cure her extensively drug-resistant TB. XDR-TB has a less than 20% chance of cure.

Her story highlights the two biggest obstacles with TB management: a lack of diagnostic tools to detect XDR-TB and the limited range of accessible drugs to treat it. It also highlights that success is possible.

Photographer: Sydelle Willow Smith

"I didn't want to be a TB statistic and that kept me going. It was a long and painful journey. Firstly, I was late diagnosed. Secondly, I was given the wrong medication for a long time. It can only be a miracle that I am still alive and cured.

At first I was diagnosed (when I was 19) with 'normal' TB, but the tablets I received didn't work. Then I was told I was multi-drug resistant. The MDR-TB drug side effects were hellish. It was a nightmare, from having skin problems, vomiting each and every day, developing pneumothorax, going through surgery, becoming deaf (thanks to a kanamycin injection).

I had 20 tablets every day for three years, that's almost 20,000 drugs of all sorts of sizes and colours. You have to be very brave to stand up to all of this. I saw many dead bodies while I was at Brooklyn Chest Hospital, and I made it a dare that I wouldn't exit those gates in a body bag.

From all of these side effects, even losing my hearing, I managed to pull through. Linezolid was the key player in my recovery, without it I am not sure if I would still be here. But, not many patients are as lucky as I was to get access to linezolid, since it is too expensive. Each tablet costs close to ZAR 700.

Linezolid needs to be made cheaper so that many more patients can have access to it. Out of 300 patients in Khayelitsha, only 22 are able to get it from MSF, what about the rest? Don't they also deserve it?"

This story is edited from a speech given by Phumeza in October 2013. For several years, many DR-TB patients were unable to benefit from the drug linezolid while it was under patent, and priced at over ZAR 700 per 600mg tablet. The patent expired on linezolid in August 2014, and the subsequent market entry of one generic company has seen public sector prices fall – though they could fall further if additional generic competitors are registered.

Resources

Photographer: Ton Koene

DATA SOURCES: *

1. Data on medicine availability in the public sector was collected from the National Department of Health's Master Procurement Catalogue, which is regularly updated on the National Department of Health's website. A limitation of this method is that medicines that are procured provincially and available in some provinces are not reflected on this list. All prices included in this report were sourced from the 1 December 2015 price list and include VAT.**

2. Data on medicine availability in the private sector was collected from the open access medicine price registry which provides data on all medicines supplied in the private sector. All prices included in this report were sourced from the medicines price registry published on 18 November 2015 and include VAT.**

3. Data on patents in South Africa was collected from the Companies and Intellectual Property Commission's (CIPC) online patent database: http://patentsearch.cipc.co.za/patents/patentsearch.aspx
Given the suboptimal search functions of the CIPC database, patent information on the CIPC database was generally found by cross-checking patent data collected from other online patent databases (including: the Orange Book, Patentscope, Espacenet, AusPat and Google Patents) on the CIPC database. We have only included pending or granted patents applied for by the company marketing an originator product, or a related company in this report.
We have not included lapsed patents in this report, as they do not block the sale of competitor products. However, many lapsed patents were identified on the medicine case studies included in this report, indicating that companies commonly file frivolous applications and later make decisions regarding whether or not to pursue claims on the basis of commercial motivations.

4. See previously published data of the Fix the Patent Laws Campaign at http://www.fixthepatentlaws.org/?p=911

5. Data on pharmaceutical companies' earnings on medicines during 2013 was sourced from IMS Health. Available via request from http://www.imshealth.com/portal/site/imshealth**

6. Data regarding the top drivers of pharmaceutical expenditure in the private sector was sourced from IMS Health, as well as the 2013 and 2014 Mediscor Medicines Reviews which are available at http://www.mediscor.net/medreviewrequest.htm

7. Data on the WHO essential medicines list was sourced from the WHO's updated adult and paediatric essential medicines lists published in 2015. Available at: http://www.who.int/medicines/publications/essentialmedicines/en/

8. Data on generic/biosimilar availability in the US was sourced from Drug Bank. Available at: http://www.drugbank.ca/ Data on generic/biosimilar availability in other countries, as well as pending generic/biosimilar availability was sourced from a number of references, including MSF country offices, pharmaceutical newsletters, press statements and communication with companies. These references are available on request.

9. Data on prescribed minimum benefits was sourced from communication with the Council for Medical Schemes between September and November 2015.

10. Data on public sector availability was sourced from communication with public sector clinicians between September 2015 and February 2016.

11. The prices of generic medicines in India were sourced from MSF India between September and November 2015. Average exchange rates for November 2015 were used to convert Rupees (Rs) to Rands (ZAR): ZAR 1= Rs 4.67.

12. The prices of generic medicines in Canada were sourced from https://www.healthinfo.moh.gov.on.ca/formulary/SearchServlet during December 2015. Average exchange rates from November 2015 were used to convert Canadian dollars (CAD) to Rands (ZAR): CAD 1 = ZAR 10.66.

* For bracket references provided throughout text
** The average exchange rate from November 2015 was used to convert South African Rands (ZAR) to US Dollars (US$) at a rate of US$ 1 = ZAR 14.14

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Photographer: Roy Potterill

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