EXPLORING PATENT BARRIERS TO CANCER TREATMENT ACCESS IN SOUTH AFRICA: 24 MEDICINE CASE STUDIES

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Prepared by Catherine Tomlinson, Heather Moyo, Zain Rizvi, Claire Waterhouse, Salomé Meyer and Marcus Low on behalf of Fix the Patent Laws and the Cancer Alliance

CANCER ALLIANCE

Collective South African Voices for Cancer

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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. We have sought to ensure accuracy in this report to the best of our abilities through a process of peer review.

Fortunately, patent landscape transparency for cancer medicines has recently improved with the December 2017 update of the Medicines Patent Pool's MedsPal databases to include patented cancer treatments recommended as essential treatments by the World Health Organisation.

In comparing the findings of this report with the MedsPal database we identified a methodology error in version 1 of the report (published in October 2017) that will be corrected in a second version of the report and future related publications.

Version 1 of the report utilised 'Lodging date: complete' provided on the Companies and Intellectual Property Commission's online patent database as the start date for all 20-year patent periods. Version 2 of the report will use 'Lodging date: complete' as the 20-year start date for patents filed locally and 'International filing date' as the 20-year start date for patents filed via the Patent Cooperation Treaty.

If you note any further errors in the report please contact Salomé Meyer at:

Mobile: +27 79 483 3175

Email: advocacy@canceralliance.co.za

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INTRODUCTION

ABOUT THE CANCER MEDICINES REPORT

Salomé Meyer, Cancer Alliance: A2M Project Manager

The right of access to health care is enshrined in Section 27 of the Constitution with the specific proviso that government must take steps "within its available resources" to ensure such.

The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) allows government to adopt provisions in the national patent law that would protect health and improve access to biosimilar and generic competition to address unaffordable medicine prices. The price of cancer medicines in particular has soared over the last 10 years globally, making access to life saving cancer treatments for most people in low and middle-income countries (LMICs) unaffordable. The recent United Nations (UN) High Level Panel on Access to Medicine, convened in 2016 called for use of TRIPS flexibilties to improve Universal Health Coverage.

Cancer Alliance was able to step up to our advocacy mission with a grant from the Open Society Foundation (OSF) that enabled us to do this pioneering research. Not only does this report highlight specific patent challenges that impact affordability and accessibility for cancer patients. The reality of the cancer landscape remains that an overwhelming majority of patients that rely on public services are excluded from accessing these medicines.

With the outcomes of this report, Cancer Alliance will with an extension of a grant from the OSF be able to initiate our Access to Medicine (A2M) campaign over a period of two years. We will join forces with the Fix the Patent Laws (FTPL) campaign to call for urgent patent policy reform which is already in the pipeline. Our work will also include a partnership with the National Department of Health to improve access and affordability of specific cancer medicines through regulatory and policy reform. We have the experience of HIV/AIDS advocacy success - it is now time for the cancer community to STAND UP and SPEAK UP.

We need to save lives with collective action that will include a 4P partnership between Patients, Public, Private sector where the patient is first!

FOREWORD

A GROWING URGENCY FOR A SUSTAINABLE SOLUTION

Ms Malebona Precious Matsoso, Director General of the National Department of Health, South Africa

The burden of cancer in South Africa has increased and will continue to increase significantly in the next few years. This increase will result in increase in treatment, screening, diagnosis and treatment costs. Only 16,2% of South Africans who are covered by medical insurance have reasonable access to medicines for the treatment of cancer. Even those with access have been recently adversely affected due to high costs. There is limited access in the public sector due to prohibitive costs.

Access to medicines can be categorised as Therapeutic Access, Financial Access Physical Access and quality. Therapeutic means that a medicine has been developed and approved by the medicines regulatory authority in the country and is on the essential medicines list or formulary. In some instance it may be reimbursed by medical insurance. Financial access on the other hand means that medicine is unaffordable to individuals, government and medical insurance. While physical access means it is not available in facilities due to poor procurement practices, stock outs, or it is not produced in sufficient quantities. Quality in this context means patients may be diagnosed, provided with appropriate and information.

Access to medicines can be fully achieved when barriers are adequately addressed.

The experience of the Antiretroviral (ARV) therapy to improve coverage in South Africa is a good lesson for cancer treatment access.

Patent barriers to access may impact negatively on the categories described earlier. For instance when medicines are not available for therapeutic use because they are not allowed for sale in certain jurisdictions due to patent exclusion criteria this may limit access. The exclusion of anticancer medicines from reimbursement by medical schemes may lead to catastrophic expenditure. The exclusion may be due to prohibitive costs or absence of a generic equivalent to promote competition. Exclusion from the Essential Medicines List by the public sector may be both a Financial and Therapeutic Access problem.

Recent developments in the approval of a bio-similar by the medicines regulatory authority of South Africa is welcome. This is a first step in improving access to anticancer medicine. We witnessed improved coverage of the ARVs to treat HIV/AIDS, when generic competition influenced prices downwards. It is our fervent hope that the same will be experienced with anticancer treatments.

The Intellectual Property Policy Framework presents an opportunity to have a sustainable solution and an opportunity to implement the recommendations of the High Level Panel on Access to Medicines. South Africa can with this policy implement patentability criteria consistent with the TRIPS agreement. We can introduce good practices in patent examination processes and ensure quality patents are granted. Access to quality medicines is possible. It can be done. Lives can be saved.

FOREWORD

HIV TREATMENT ACCESS SHOWS IT IS POSSIBLE FOR CANCER TOO

Dr Andrew Hill PhD, Senior Visiting Research Fellow, Department of Translational Medicine, University of Liverpool

When countries find out how cheaply drugs can be made, this can change the whole vision for how diseases could be treated. We could achieve Universal Access to treatment for all Essential Medicines if we could lift patent restrictions and mass produce generic drugs at low prices. In South Africa, antiretroviral treatment is available to anyone with HIV infection. Can we do the same for treatment of most cancers?

In 2002, a year of treatment for HIV/AIDS was being sold for $10,000 - this price has now fallen to $75, after patent restrictions were overcome and the drugs were mass produced by generic companies. Worldwide, over 20 million people are receiving low-cost generic treatment for HIV, saving millions of lives. This is only possible because patents have been removed, allowing mass production of low cost generics. The treatment of HIV/AIDS is one of the great success stories in modern medicine.

However the success story of treating HIV/AIDS should not stand alone, but be repeated for a wide range of diseases, including cancer, TB, viral hepatitis and diabetes. Almost all medicines can be manufactured for very low costs, but many are sold for very high prices. When patents are enforced on drugs, this allows pharmaceutical companies to exploit their monopoly position and charge high prices.

As this report shows, the prices of many cancer drugs in South Africa are far higher than in India, where generics are available. In the most extreme case, a year's supply of lenalidomide is priced at ZAR 882,000 in South Africa and less than ZAR 32,000 in India.

The South African government is allowing patents to be granted on many cancer drugs, which then allows pharmaceutical companies to charge high prices, which can be a barrier to access. As a result, it could be very difficult for the South African Health Department to afford Universal Access to treatment for most cancers. It is not clear whether South Africa benefiting at all from allowing so many secondary patents to be granted. However it is clear that the high prices which result from patent restrictions can prevent people being treated with life-saving medicines.

This report should make the South African government to re-consider their approach to patented versus generic medicines. If we want to make major advances in treatment coverage, treating far more people for cancer in South Africa. However for this to be possible, drug prices have to fall. South Africa and India already pay similar prices for drugs to treat HIV/AIDS. So why should South Africa continue to pay far higher prices for many drugs to treat cancer? Patent restrictions need to be reviewed carefully. Where patents are restricting access to cancer drugs, prices should be lowered immediately, or compulsory licenses enforced.

We have already learned a great deal about ensuring access to medicines, from the past 17 years of the HIV epidemic. Now it is time to use our new knowledge to achieve a transformation in the treatment of cancer and other diseases.

FOREWORD

REPORT SHOWS THE PERVERSE CONSEQUENCES OF A FAILED PATENT SYSTEM

Professor Yousuf A Vawda, Honorary Research Fellow, University of KwaZulu-Natal, South Africa

This is a timely report in the context of the growing cancer epidemic in South Africa and sub-Saharan Africa, and the glacial pace at which the project to reform our patent laws to a pro-access, public-health oriented intellectual property policy is proceeding. If ever South Africans and indeed the government needed a reminder of the both the public health crisis posed by the lack of access to cancer medicines because of patent-based monopoly pricing, and the need for urgency in reforming our legal framework, this is it.

The report is an evidence-based and comprehensive piece of research, given the limitations of easily accessible information on patent grants, and is well-written and readable. The patent status and accessibility of twenty four key cancer medicines are analysed, and the verdict is telling: South Africa is not using the policy space permitted by international law to make medicines accessible to its people; it is routinely granting unwarranted patents, which many other countries are rejecting; that this has meant that patent holders have forced monopoly pricing on us, thereby denying patients both in the private, but particularly the public, sector life-saving medicines.

It reminds us of how easy it is to obtain secondary patents in South Africa, and the perverse consequences that follow. The report highlights the example of the drug rituximab whose patent expired (after 20 years of protection from competition) in 2004. But thanks to the ease with which secondary patents are granted under South Africa's non-examining 'depository' system, the patent holder's monopoly protection will extend to (for the moment) until 2030 – 42 years after the first patent on this drug was granted in South Africa. If this does not tell us that our patent system is broken, then nothing will!

The central message in this vital study is that South Africa should move with great speed to put into place a legal framework that enables us to access quality, affordable medicines to treat the growing numbers affected by cancer and other life-threatening conditions. It proposes that the 3 important mechanisms to facilitate this are: setting strict criteria for the grant of a patent, and the substantive examination of applications; permitting opposition to patent grants by interested persons to weed out unworthy patents; and a workable system to grant compulsory licences, a most powerful tool to override the patent holder's rights and force competition in the market. While these are not the only flexibilities available to enhance access, they represent a solid foundation on which to establish a patent system for pharmaceuticals that is balanced, fair to both patent holders and consumers, and one which meets the constitutional obligation to realise access to medicines and health care for all the people of South Africa.

FOREWORD

CANCER AND INTELLECTUAL PROPERTY – BREAKING THE DEADLOCK

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

There is probably no diagnosis which so deserves the label of "dread" than that of cancer. Regardless of the evidence of progress in diagnosis and treatment, any person faced with a diagnosis of cancer is immediately faced with fears of death and suffering, preceded by inhumane adverse effects associated with the treatment. That such fears should also include very real concerns about whether the treatment will be available or affordable merely adds to the burden.

Recent years have seen remarkable progress in at least some cancers affecting children and adults. Other cancers remain challenging, even though there may be some benefits from new forms of management, including new medicines. The tragedy is that, all too often, fears of being denied access are real. Health systems, whether funded publicly or privately, face serious problems assessing the value of new and expensive cancer treatments and even more problems with the prices demanded by their manufacturers. Many of the new treatments are complex, large, biological molecules, for which access to follow-on "biosimilar" versions is delayed even longer than expected.

Although used to treat an adverse effect associated with the use of chemotherapeutic agents, the immune stimulant filgrastim provides an object lesson. The first originator version was registered in South Africa in 1992, yet the first biosimilar was only registered in 2017, 25 years later.

The Lancet Commission on Essential Medicines Policies has noted that every country needs to implement a comprehensive set of policies to ensure the affordability of essential medicines.[1] Included in that policy set must be deliberate polices addressing intellectual property, and ensuring that each of every one of the flexibilities provided for by international agreements can be used effectively. There also have to be continued efforts to develop and implement new systems of innovation that delink the cost of research from the eventual prices demanded for new essential medicines. In South Africa, issues related to intellectual property are not considered by the national medicines regulatory authority when considering an application for registration. As the new South African Health Products Regulatory Authority is brought into effect, that policy stance needs to be protected and maintained.

This ground-breaking study uncovers the way in which South Africa's current patent laws influence access to 24 selected cancer medicines. It provides a potent argument for completing the reform of those laws, a process which has already been unduly protracted. As the authors clearly state: "Thousands of people living with cancer in South Africa cannot afford to wait any longer".

USEFUL TERMS

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.

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 closely comparable in terms of safety and efficacy.

Compulsory license: A license given by the government that allows someone to produce a patented product without the consent of the patent owner.

Clone: Rebranded versions of originator medicines launched by the patent holder, 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]

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 originator medicines.

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.

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.

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). Types of patents regularly granted on pharmaceutical products include primary patents granted on a new chemical compound or biologic entity and, more commonly, secondary patents granted on:

1. **Combinations:** patents claiming protection on the combination of two or more chemical compounds and/or biologic entities;
2. **Composition:** patents claiming protection on a specific composition/formulation/ preparation of a chemical compound/biologic entity for its administration (i.e. dosage, tablet, slow release, paediatric formulation);
3. **Markush claims:** patent claims on generic chemical symbols that generally cover a broad range of chemical compounds and may provide protection on multiple applications and variations thereof;

4. **Method of preparation:** patents claiming protection on the method of synthesising, acquiring or manufacturing the active ingredients and/or manufacturing the pharmaceutical product;
5. **Method of use**: patents claiming protection on the use of a chemical compound and/ or biologic entity for preventing, diagnosing or treating a health condition;
6. **Polymorph, Isomer, Prodrug, Ester, Salts ("PIPES"):** patents claiming protection "on minor modifications to the structure or chemical makeup of a molecule"[2]; and
7. **Selection:** patents claiming protection on a specific component or element contained in a previously granted "parent" patent.

Patentability Criteria: A list of conditions that an invention must satisfy to be patentable. These typically include standards of novelty, inventiveness, and industrial applicability.

South African Essential Drug Lists (SA EDLs): Lists of medicines that are intended to be available within the public healthcare system at the indicated level of care (primary, hospital or tertiary and quaternary) and for the indications for which they are listed as essential.

South African Tertiary and Quaternary Essential Medicines Recommendations: A list of recommendations of treatment for certain indications that must be available to patients seeking care at a tertiary or quaternary facility.

Small molecule medicines: Medicines whose active ingredients are chemically manufactured.

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 mandating minimum standards of intellectual property protection, while preserving important safeguards for public health.

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.

WHO: World Health Organisation.

WHO EML: The Essential Medicines List of the WHO recommends medicines that "are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford."[3]

EXECUTIVE SUMMARY

Cancer rates in South Africa are expected to rise significantly over the next two decades.[4] In sub-Saharan Africa, the number of new cancer cases is expected to increase by more than 85% from 2008 to 2030.[5] By then, for every four deaths from HIV/AIDS in the region, there will be three deaths from cancer.[6] Along with a growing cancer burden, states will be confronted with rising and unaffordable prices for cancer medicines.

For example, while the volume of oncology medicines procured in South Africa remained the same between 2015 and 2016, private medical insurers spent an increasing share of their medicine expenditure on oncology treatments – from 8.8 to 9.3%.[7] Specialty medicines, in particular, pose a significant burden. One report found that specialty medicines used in oncology had an average cost of ZAR 23,533 per item in 2016.[8] Indeed, oncology specialty medicines accounted for only 13% of specialty medicines by volume, but made up 31% of expenditure for all specialty medicines.

This study seeks to investigate how South Africa's patent laws influence access to cancer medicines by analysing the patent status and length, affordability of, and access to 24 case study medicines. Our research demonstrates that South Africa routinely grants and upholds patents that could have been challenged and rejected if South Africa adopted strong patentability criteria, patent examination processes and opposition procedures. **Overlapping secondary patents create significant legal uncertainty regarding the patent status of medicines, dis-incentivise the entry of generic or biosimilar products, and hinder the affordability and accessibility of the medicines to patients in need.**

While the 24 medicines were not randomly selected, they represent a large sample that illustrates certain characteristics of the patent system in South Africa and the relationship between domestic patent laws and medicines pricing and access.

PATENT STATUS AND LENGTH

- **We found a total of 92 secondary patents on the 24 cancer medicines in our study.** 74 were active secondary patents and thus potentially competition-blocking in South Africa.
- **Of the total 92 secondary patents granted, 39 were rejected or withdrawn in at least one other jurisdiction.** Secondary patents were composed of compositions (26), Markush claims (23), methods of use (17), methods of preparation (13), polymorph/isomer/ prodrug/ester/salts (11), combinations (8), selection patents (4) and other (3). (Some were classified in multiple categories).
- **An additional 17 patents on these medicines were pending or accepted in South Africa, 6 of which had been rejected or withdrawn in at least one other jurisdiction.**
- Secondary patents can significantly extend the length of monopoly protection beyond the 20 years mandated by international law. For example, the primary patent on rituximab expired in 2004, but it will be protected by secondary patents until at least 2030 – or 42 years after the first patent was granted in South Africa.

AFFORDABILITY

- **Of the 24 medicines, 15 are available in India for less than half of the price offered to the South African private sector.** In the most extreme case, a year's supply of lenalidomide is priced at ZAR 882,000 in South Africa and less than ZAR 32,000 in India.
- **10 medicines that are not available in the South African public sector – likely due to their cost – are available in India for less than half the price offered to the South African private sector.**

ACCESSIBILITY

- **Of the 24 case study medicines, 21 are available in the private sector in South Africa and only 7 are available in the public sector**. (Some additional ones may be available in specific public sector hospitals where budgets allow.) Of the 24 medicines in our study, 10 are on the WHO's Essential Medicines List (EML) and only 4 of the 24 are on South Africa's Essential Drugs List (EDL).
- **Our analysis suggests that the lack of public sector availability of these drugs is driven mainly by high prices which, in turn, are caused by the proliferation of poor quality patents.**

In other jurisdictions, poor quality patents are commonly rejected or withdrawn during examination or via opposition procedures. In South Africa, neither

mechanism exists. Instead, the only mechanism to challenge patents is through undertaking litigation after a patent has been granted. Our research, however, highlights that patent litigation in South Africa is rare and thus many weak patents remain in force.

Currently there is zero onus on monopoly holders to demonstrate and deliver novel innovation as a prerequisite for receipt of extended commercial monopolies. Rather, the burden to disprove the validity of weak patents falls on third parties – such as patient groups or competitors – through undertaking expensive and lengthy litigation against the monopoly holder. This bias of South Africa's patent system towards monopoly holders is at odds with government's Constitutional obligation to take reasonable legislative steps to protect and promote the right to health of people living in South Africa. It is also particularly troubling given the disconnect between the cost of developing drugs and subsequent profits: a recent study found that the average, risk-adjusted cost to develop a cancer drug was $648 million, while the median revenue was $1658 million.[9]

In 2016 United Nations (UN) Secretary-General Ban Ki-Moon's High-Level Panel on Access to Medicines set out recommendations to improve medicine access and promote innovation to address health needs. The High-Level Panel called on countries to fully utilise flexibilities to protect health contained within the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS).[10] TRIPS, which was adopted in 1995, requires World Trade Organisation (WTO) members to provide minimum standards of intellectual property protection, including 20-year patent terms on inventions. But the agreement also preserved important safeguards, or flexibilities, that states could utilise to protect health.

To date, South Africa has not fully taken advantage of these flexibilities. To improve medicine access, address the growing cancer epidemic, and remedy the bias in favour of monopoly holders, South Africa should follow the HLP's recommendations and fully implement TRIPS flexibilities. In the short-term, South Africa must implement existing TRIPS flexibilities to reduce the exorbitant prices of cancer medicines, and increase access to lifesaving treatment. These include granting compulsory licenses, and importing cheaper, patented products from other countries (i.e., parallel importation).

For instance, if South Africa issued compulsory licenses on cancer medicines lenalidomide and sorafenib, the prices of these medicines could be reduced by more than 90% through accessing generics at prices available on par with those available in India. At lower prices, the public sector could offer these medicines, substantially increasing access to cancer treatment.

Going forward, South Africa must urgently revise its intellectual property policy to protect and promote medicine access by:

1. Setting stringent patentability criteria to limit the granting of patents to only genuine innovations (i.e., excluding mere new formulations or new uses of existing medicines from patentability);
2. Introducing examination and opposition procedures to ensure patentability criteria is met; and
3. Developing easy-to-use, workable procedures for granting compulsory licenses.

Notably, the South African government has made commitments to adopting and implementing these reforms in the recently released 2017 Draft Intellectual Property Policy. To improve medicine access in the country, government should urgently finalise this policy and introduce bills to reform the Patents Act and other health-related intellectual property legislation. Above all, the government must implement these TRIPS flexibilities, lest they remain words on paper. Thousands of people living with cancer in South Africa cannot afford to wait any longer.

BACKGROUND

The TRIPS agreement, which was adopted in 1995, requires WTO members to provide minimum standards of intellectual property protection, including 20-year patent terms on inventions. But the agreement also preserved important safeguards, or flexibilities, that states can utilise to protect health.

In 2016 UN Secretary-General Ban Ki-Moon's High-Level Panel on Access to Medicines set out recommendations to improve medicine access and promote innovation to address health needs. The High-Level Panel called on countries to fully utilise the TRIPS flexibilities to protect health.[11]

Following TRIPS adoption, sky-rocketing rates of secondary patenting on pharmaceuticals were observed in developed and developing countries.[12],[13],[14] According to a report by the European Commission, during the 1980s pharmaceutical products were generally only protected by a single primary patent on a medicine's base compound. Yet in the 1990s the number of patents granted on individual medicines soared as companies sought multiple secondary patents on medicines as part of a "tool-box" of strategies to extend their commercial monopolies beyond 20-years.[15] Secondary patents are typically claimed on new formulations, dosages, uses and combinations of existing chemical compounds and/or biologic entities. In its report, the UN High-Level Panel highlighted that "secondary patents can create legal uncertainty around the patent status of a health technology, which in turn discourages entities from procuring generic versions of products for fear of patent infringement."[16] A number of countries, including Argentina and India, have changed their domestic laws and regulations to reduce the number of poor quality secondary patents granted in their countries—often excluding new formulations and/or new uses of existing medicines from patentability.

Research demonstrates that secondary patents are often granted on weak claims of novelty and inventiveness[17], many of which fail to block the entry of generic competition when challenged in court,[18] or are 'worked around' by generic competitors.[19] Yet, when routinely granted, such secondary patents increase competitors' risks of facing expensive infringement proceedings when seeking to introduce their products. In short, the considerable uncertainty added by secondary patents can delay the availability and the use of cheaper generic alternatives, thereby inhibiting medicine access and driving up health care costs long after primary patents have expired.[20,21]

To address the negative consequences of secondary patenting on medicine access, the UN High-Level Panel recommended that countries fully adopt TRIPS flexibilities into their national laws and implement them in practice.

Flexibilities available under TRIPS include (among others):

1. Setting stringent patentability criteria to limit the granting of patents to only genuine innovations (i.e., excluding mere new formulations or new uses of existing medicines from patentability);
2. Introducing examination and opposition procedures to ensure patentability criteria is met; and
3. Developing easy-to-use, workable procedures for granting compulsory licenses.

In all of these areas, South Africa currently falls short. Despite government commitments to implement patent examination procedures, South Africa does not currently undertake any substantive examination of patent applications to ensure that any patentability criteria have been met prior to the granting of patents, nor does it provide for opposition of patents by third parties.[22] Presently the only way to challenge a patent in South Africa is through litigation—generally a lengthy and prohibitively expensive process.[23] Lacking a patent examination system, South Africa also consequently lacks explicit guidelines for examining patentability of pharmaceutical products and processes. These guidelines would act to not only guide patent examiners but also reduce any legal ambiguities regarding patentability of secondary claims.

Without patent examination or opposition procedures in place, and with lax patentability criteria, South Africa is an outlier with regards to its high rate of granting patents. In a comparison of matching pharmaceutical patent applications filed in a number of countries between 2000 and 2002, Sampat and Sheldon found that South Africa granted 93% of patents applied for, versus 61% in the US, 51% in Europe and 29% in Japan. The authors noted that "since South Africa does not examine applications the only applications not granted there are those withdrawn during the examination process due to failure to pay issue fees, and (a very small number) applications still pending".[24]

In this study, we investigate how South Africa's patent laws influence patent status and the length of market exclusivity for 24 cancer medicines. We also explore the impact of patent status and the period of exclusivity on affordability and accessibility of the case study medicines and consider the impact of South Africa's patent laws on health and medicine expenditure. We summarise our findings in the analysis section.

METHODOLOGY

To explore how South Africa's patent laws and processes influence pharmaceutical patenting in the country, we compared the status of patents granted in South Africa on our 24 case study medicines with matching patents in other jurisdictions.

In particular, we assessed whether patents granted in South Africa were withdrawn or rejected in other jurisdictions. Data regarding patents granted in South Africa was extracted from the **Companies and Intellectual Property Commission**'s (CIPC) searchable online patent database. After extracting patent data from the CIPC, we compared the status of matching patents applied for in other jurisdictions through reviewing each patent's 'National Phase: National Status' on Patentscope (the publicly searchable database of WIPO) on patents for which a PCT (Patent Cooperation Treaty) number was available. We also conducted Google searches of patent litigation related to the case study medicines.

For the purposes of this study, we did not conduct exhaustive patent searches for the case study medicines. Rather, we sought to identify patents perceived as potentially blocking the use of competitor products. Lapsed patents and patents granted to competitors are not considered in our analysis. Instead, we focused on identifying potentially blocking patents granted to the commercial monopoly holder or a related company or research institution. While we undertook extensive patent searches to identify potentially blocking patents, some relevant patents may not have been identified as companies are not required to include related medicines' names in the abstract or title of patent applications.

Using guidelines developed by the United Nations Development Program and South Centre on pharmaceutical patenting, patents were categorised into common categories of pharmaceutical and chemical patents.[25] Because of the lack of transparency—and the tactics used by pharmaceutical companies to create ambiguity and hide information on patent status—this approach is necessarily a best available approximation.

To explore the impact of South Africa's patent laws and procedures on generic availability in the country, we considered generic availability in South Africa versus India, the US, Canada and the EU. India was selected as a comparator country because it has been a global leader in adopting and utilising health safeguards allowed under TRIPS to protect access to medicine and support growth of its local industry. Canada, the US and EU were selected to allow for comparison of generic availability in wealthy countries with stringent regulatory authorities, and because data on generic availability in these jurisdictions is easily searchable via the Drugbank.com database.

A limitation of our study was that we could not assess the impact of regulatory delays on generic availability in South Africa as data on pending regulatory applications is not publicly available.

To explore the impact of South Africa's patent laws and procedures on medicine affordability, we compared the costs of cancer treatment in South Africa with generic prices (when available) in India and Canada. Generic prices from India were considered as the country has proactively adopted TRIPS health safeguards into its patent laws, and private sector medicine prices could be easily sourced online via 1mg.com and drugsupdate.com. Canada was selected as a comparator country, as its online drug benefit formularies provide data on generic prices in the country.[26] [27]

Generic prices from India were sourced from 1mg.com and drugsupdate.com during July 2017 and an exchange rate of INR 4.92=ZAR 1 was used to convert Indian Rupees to South African Rands. Generic prices from Canada were sourced from the Ontario Drugs Benefit Formulary during July 2017 and converted from Canadian Dollars to South Africa Rands at an exchange rate of CAD1=ZAR9.92. Finally, private sector prices for South Africa were sourced from the 27 March 2017 Database of Medicine Prices downloaded from the Medicines Price Registry and public sector prices were sourced from the National Department of Health's (NDOH) 7 July 2017 Master Procurement Catalogue.

A limitation of this study is the lack of robust comparisons of medicine costs across multiple jurisdictions due to a lack of transparent global medicine pricing data.

We then considered the impact of medicine affordability on accessibility. To consider the impact of generic or biosimilar availability on medicine accessibility in the public sector, we considered whether case study medicines were procured nationally for public sector use through assessing their inclusion on the NDOH's Master Procurement Catalogue. While national procurement is a good indicator of public sector medicine availability,

a limitation of this method is that it does not account for provincial or facility level procurement which may allow some public sector users to access medicines under limited circumstances. A further limitation of this measurement of accessibility is that it does not consider other barriers to access within the public sector, such as inaccessibility of public facilities and diagnostic services, as well as medicines shortages.

All medicine indications were sourced from the 2015 South African Medicines Formulary, except where separate references are provided. Data regarding essential medicine statuses were sourced from the 2017 World Health Organisation Essential Medicines Lists and South Africa's 2017 Tertiary and Quaternary Essential Medicines Recommendations.

Finally, where data was available, we synthesized our findings to present an overview of the patent landscape and its impact on affordability and accessibility of cancer medicines.

The 24 case study medicines included in our study are listed in Table 1. Table 1 also identifies the type(s) of cancers the medicines are predominately used to treat.

Only medicines for which generic products in South Africa were unavailable at the start of the study were eligible for inclusion in this analysis. During the study period, a generic competitor was introduced for one of the case study medicines (bortezomib). In addition to generic availability, we also considered the following in selecting case study medicines:

- whether the medicine was identified as essential by the WHO;
- whether the medicine was identified as a cost driver by the National Essential Drugs Programme[28] and/or Mediscor PMB's annual Medicines Review[29]; and
- whether the medicine was identified as a medicine for which prices (or other factors) inhibit access in South Africa through communication with cancer NGOs and/or the Cancer Alliance's surveys circulated to oncologists and people living with cancer.[30]

Table 1: 24 Case Study Medicines

	Type of Cancer	Medicine Name
1	Multiple myeloma	Thalidomide
2		Lenalidomide
3		Bortezomib
4	Leukaemia and Lymphoma	Bendamustine
5		Daunorubicin
6		Dacarbazine
7		Dasatinib
8		Nilotinib
9		Rituximab
10		Asparaginase
11		Pegaspargase
12	Non-small lung cancer	Erlotinib
13		Crizotinib
14	Breast cancer	Trastuzumab
15		Trastuzumab emtansine
16		Lapatinib
17	Prostate cancer	Abiraterone acetate
18		Enzalutamide
19	Melanoma	Ipilimumab
20	Kidney, liver and thyroid cancer	Sorafenib
21	Anti-VEGF therapy	Bevacizumab
22	Symptoms associated with certain cancers and treatment	Octreotide
23		Filgrastim
24		Pegfilgrastim

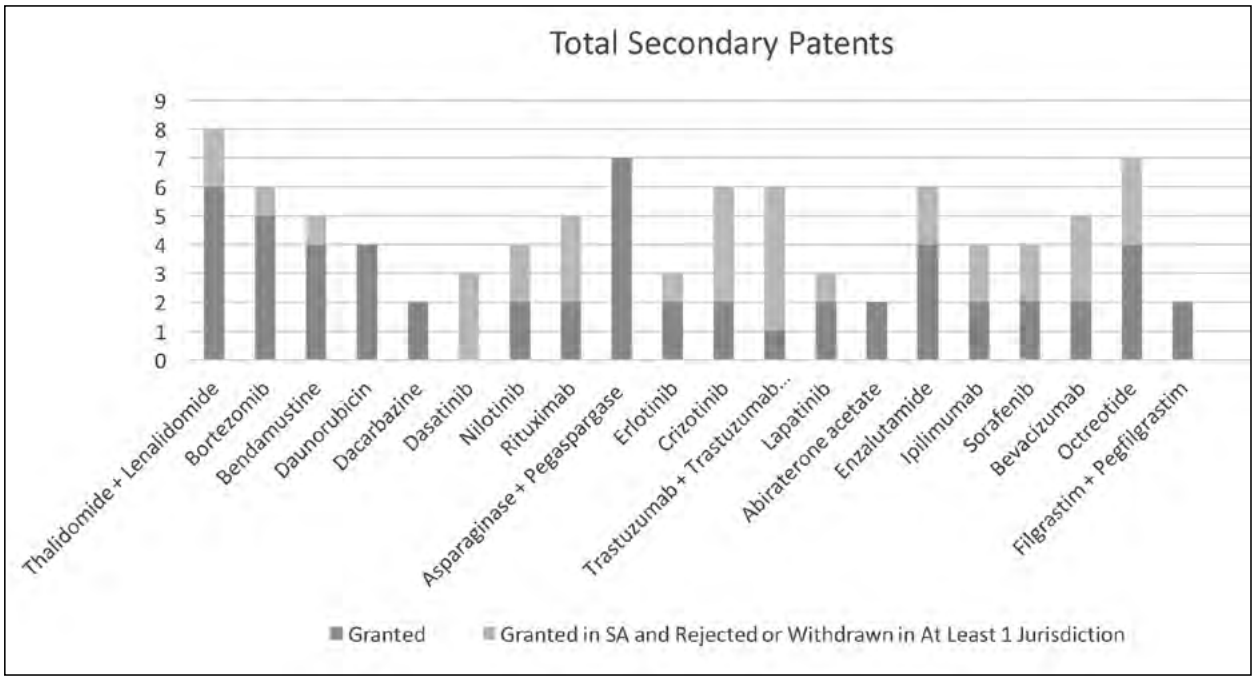
ANALYSIS

Our research demonstrates that South Africa routinely grants and upholds patents that could have been subject to challenge and rejected if the government adopted strong patentability criteria, patent examination processes and opposition procedures. While the 24 medicines analyzed were not randomly selected, they represent a large sample that illustrates certain characteristics of the patent system in South Africa and the relationship between domestic patent laws and medicines pricing and access.

PATENT STATUS AND LENGTH

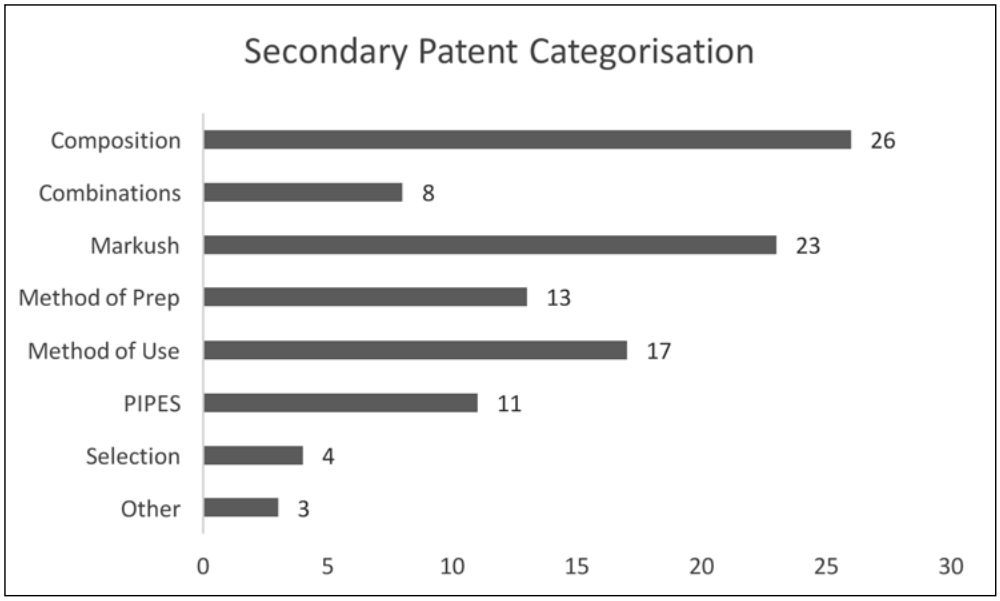
We found a total of 92 secondary patents on the 24 cancer medicines in our study. 74 were active secondary patents and thus potentially competition-blocking in South Africa. Of the total 92 secondary patents, 39 were rejected or withdrawn in at least one other jurisdiction.

Figure 1: Total Secondary Patents



Secondary patents were composed of compositions (26), Markush claims (23), methods of use (17), methods of preparation (13), polymorph/isomer/prodrug/ester/salts (11), combinations (8), selection patents (4) and other (3). (Some were classified in multiple categories). An additional 17 patents were pending in South Africa, 6 of which had been rejected or withdrawn in at least one other jurisdiction.

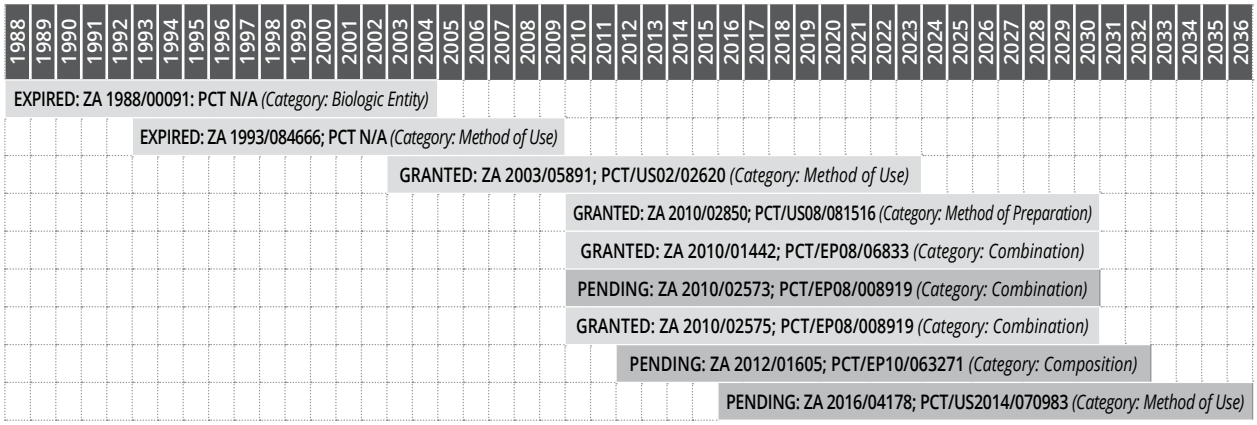
Figure 2: Secondary Patent Categorisation



**Categorised patents add up to more than 92 because some patents were classified in multiple categories.*

Secondary patents can significantly extend the length of monopoly protection beyond the 20 years mandated by TRIPS. For example, the primary patent on rituximab expired in 2004, but it will be protected by secondary patents until at least 2030 – or 42 years after the first patent was granted in South Africa. If a pending secondary patent application is granted, the monopoly protection will extend to 2036 for a total of 48 years.

Figure 3: Patent Timeline for Rituximab



Together, these secondary patents create significant legal uncertainty regarding the patent status of medicines, dis-incentivie the entry of generic or biosimilar products, and hinder the affordability and accessibility of the medicines to patients in need.

AFFORDABILITY

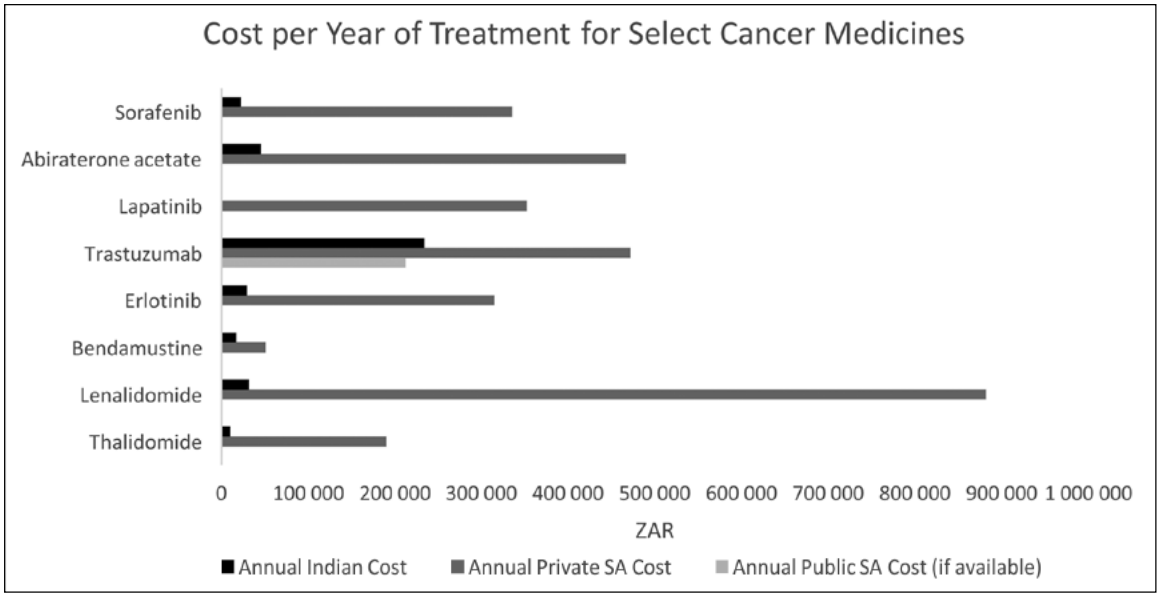
Of the 24 case study medicines, 10 are available in India for less than a quarter of the price offered to the South African private sector, and 15 are available in India for half the price or less. 10 medicines that are not available in the South African public sector – likely due to their cost – are available in India for less than half the price offered to the South African private sector.

Table 2: Unit Prices of 24 Case Study Medicines (ZAR)

	Medicine Name	SA Private Sector Price	SA Public Sector Price	Indian Price
1	Thalidomide	130	Not available	8
2	Lenalidomide	3308	Not available	30
3	Bortezomib	10994	Not available	2540
4	Bendamustine	4182	Not available	1304
5	Daunorubicin	515	93	81
6	Dacarbazine	204	Not available	63
7	Dasatinib	728	Not available	Not available
8	Nilotinib	243	17	Not available
9	Rituximab	3365	1590	1016
10	Asparaginase	1327	Not available	188
11	Pegaspargase	NA	Not available	Not available
12	Erlotinib	736	Not available	64
13	Crizotinib	NA	Not available	Not available
14	Trastuzumab	23562	10596	11687
15	Trastuzumab emtansine	NA	Not available	Not available
16	Lapatinib	161	Not available	Not available
17	Abiraterone acetate	319	Not available	30
18	Enzalutamide	266	Not available	Not available
19	Ipilimumab	4805	Not available	Not available
20	Sorafenib	229	Not available	12
21	Bevacizumab	4440	2784	5030
22	Octreotide	218	93	40
23	Filgrastim	1493	464	456
24	Pegfilgrastim	8544	Not available	1728

In the long-run, the high prices of cancer medicines pose a significant and unsustainable burden on the South African health system, diverting scarce resources away from other pressing needs. These prices are not inevitable, but instead reflect the largely unchecked ability of pharmaceutical companies to charge what the market will bear. In the most extreme case, a year's supply of lenalidomide is priced at ZAR 882,000 in South Africa and less than ZAR 32,000 in India. These prices are also likely not linked to the cost of developing these drugs: a recent study found that the average, risk-adjusted cost to develop a cancer drug was $648 million, while the median revenue was $1658 million. [31]

Figure 4: Annual Cost for Select Cancer Medicines



**This figure includes all case study medicines for which treatment and pricing information was available. With the exception of trastuzumab, the public sector did not offer any of the medicines.*

ACCESSIBILITY

Our research highlights significant gaps in access to cancer medicines in South Africa. Of the 24 case study medicines, 21 are available in the private sector in South Africa and only 7 are available in the public sector. (Some additional ones may be available in specific public sector hospitals where budgets allow.) Of the 24 medicines in our study, 10 are on the WHO's Essential Medicines List (EML) and only 4 of the 24 are on South Africa's Essential Drugs List (EDL). 4 medicines deemed essential by the WHO are unavailable in the public sector in South Africa, despite the fact that cheap Indian generics exist for 3 of them.

Table 3: Accessibility of 24 Case Study Medicines

	Medicine name	WHO EML*	SA EDL**	Available in Public Sector	Available in Private Sector	Generics available in SA	Generics available in India	Generics available in the US, EU or Canada
1	Thalidomide	No	No	No	Yes	No	Yes	No
2	Lenalidomide	No	No	No	Yes	No	Yes	No
3	Bortezomib	No	No	No	Yes	Yes	Yes	Yes – EU
4	Bendamustine	Yes	No	No	Yes	No	Yes	No
5	Daunorubicin	Yes	No	Yes	Yes	No	Yes	Yes – US
6	Dacarbazine	Yes	No	No	Yes	No	Yes	Yes – US
7	Dasatinib	Yes	No	No	Yes	No	No	No
8	Nilotinib	Yes	Yes	Yes	Yes	No	No	No
9	Rituximab	Yes	Yes	Yes	Yes	No	Yes	Yes – EU[32]
10	Asparaginase	Yes	No	No	Yes	No	Yes	No
11	Pegaspargase	No	No	No	No	No originator or generic available	No	No
12	Erlotinib	No	No	No	Yes	No	Yes	Yes – Canada
13	Crizotinib	No	No	No	No	No originator or generic available	No	No
14	Trastuzumab	Yes	Yes	Yes	Yes	No (clone available)	Yes	No
15	Trastuzumab emtansine	No	No	No	No	No originator or generic available	*No*	*No*
16	Lapatinib	No	No	No	Yes	No	No	No
17	Abiraterone acetate	No	No	No	Yes	No	Yes	No
18	Enzalutamide	No	No	No	Yes	No originator or generic available	No	No
19	Ipilimumab	No	No	No	Yes	No	No	No
20	Sorafenib	No	No	No	Yes	No	Yes	No
21	Bevacizumab	Yes	No†	Yes	Yes	No	Yes	No
22	Octreotide	No	No†	Yes	Yes	No	Yes	Yes – US
23	Filgrastim	Yes	Yes	Yes	Yes	No	Yes	Yes – US, EU, Canada
24	Pegfilgrastim	No	No	No	Yes	No	Yes	No

* *Included on the World Health Organisation's 2017 Essential Medicines Lists for Adults and Children for a cancer related indication*

** *Included on South Africa's Tertiary and Quartenary Essential Drugs List for a cancer related indication*

† *Included on SA EDL, but not for cancer related indication*

High prices restrict availability of drugs in the public sector. These, in turn, are caused by the proliferation of poor quality patents that inhibit the introduction of cheaper, generics. [33] Thalidomide provides a salient example. The Department of Health acknowledged in communication that thalidomide was not available in the public sector due to its cost. Thalidomide costs ZAR 129 per 50 mg tablet in the private sector. In South Africa, eight secondary patents may block competition for thalidomide until 2026. In India, no blocking patents exist, and thalidomide is available as a generic for less than 1/16 of the price in South Africa at ZAR 8.

Lower prices – and greater access – are possible in jurisdictions like India because secondary patents are commonly rejected or withdrawn during examination or via opposition procedures. In South Africa, neither mechanism exists. Instead, the only mechanism to challenge patents is through undertaking litigation. Our research, however, highlights that patent litigation in South Africa is rare and thus many weak patents remain in force delaying the introduction of affordable generic products.

See individual medicine case studies in the pages following for more detail.

MEDICINE CASE STUDIES

1+2. THALIDOMIDE AND LENALIDOMIDE

THALIDOMIDE PRICE AND AVAILABILITY

Thalidomide is indicated for the treatment of relapsing or refractory multiple myeloma. According to email communication with the Department of Health in March 2016, thalidomide is not included on South Africa's Tertiary and Quaternary Essential Medicines List due to cost. Thalidomide is not available in South Africa's public sector, but can be accessed via the private sector.

In South Africa, only Celgene's thalidomide products are available at a cost of ZAR 129.65 per 50mg capsule. Standard multiple myeloma treatment using thalidomide involves daily 200 mg doses for as long as clinical benefit is provided. At this dose, a year of thalidomide in South Africa's private sector cost ZAR 189,289. Equivalent generic products are available in India for ZAR 9,636 for a year's treatment.

THALIDOMIDE PRICES				
Dosage and formulation	**Originator product prices in SA private sector**	**Originator product prices in SA public sector**	**Generic prices in Canada (if available)**	**Generic prices in India (if available)**
thalidomide 50 mg capsule/ tablet +	ZAR 129.65	N/A	N/A	Rs 39.38 (Hetero, Fresenius, Dr Reddy) ZAR 8.00
thalidomide 100 mg capsule/ tablet	N/A	N/A	N/A	Rs 64.96 (Hetero, Fresenius) ZAR 13.20

+ price per capsule/tablet

LENALIDOMIDE PRICE AND AVAILABILITY

Lenalidomide is a derivative of thalidomide that is more effective and has fewer side-effects than the older formulation.[34] Lenalidomide is registered in South Africa for the treatment of multiple myeloma in patients that have received at least one prior therapy. It is also indicated for the treatment of patients with myelodysplastic syndromes.

Lenalidomide is not available in the public sector and can only be accessed in the private sector. Currently only Celgene's originator lenalidomide product sold under the brand name Revlimid is available in South Africa. Prior to the registration of patented Revlimid, private sector multiple myeloma patients in South Africa could access generic lenalidomide from India via Section 21 Authorisations. However, following registration of Celgene's patented product[35], Section 21 Authorisations for import of generic lenalidomide were cancelled and subsequent requests for authorisation were rejected. The rejection of Section 21 applications to import generic lenalidomide into South Africa is currently being challenged on the basis that the patented product is inaccessible due to its high price. The MCC has previously granted Section 21 Authorisations for the importation of HIV and TB treatments when the high cost of patented products prevented access.[36]

Lenalidomide is generally taken for 3 weeks (21 days) – followed by one week off treatment – starting at dosages of 25mgs. Lenalidomide treatment should continue for as long as clinical benefits are provided.[37] In South Africa, a year of 25mg Revlimid treatment costs ZAR 882,000. In India, where generic products are available, a year of 25mg lenalidomide treatment costs ZAR 31,588.

LENALIDOMIDE PRICES				
Dosage and formulation	**Originator product prices in SA private sector**	**Originator product prices in SA public sector**	**Generic prices in Canada (if available)**	**Generic prices in India (if available)**
lenalidomide 5 mg capsule +	ZAR 3,308	N/A	N/A	Rs 146.20 (Natco) ZAR 29.72
lenalidomide 10 mg capsule +	ZAR 3,500	N/A	N/A	Rs 299.20 (Natco) ZAR 60.81
lenalidomide 15 mg capsule +	ZAR 3,500	N/A	N/A	N/A
lenalidomide 25 mg capsule +	ZAR 3,500	N/A	N/A	Rs 616.71 (Natco) ZAR 125.35

+ price per capsule/tablet

PATENTS GRANTED ON THALIDOMIDE AND LENALIDOMIDE IN SOUTH AFRICA

The earliest identified patent granted on thalidomide in the United States was filed in 1955 (US2830991 A). Our research did not identify a matching patent applied for in South Africa. In 1998, Celgene acquired exclusive worldwide rights to thalidomide patents. The core compound patent on lenalidomide was filed by Celgene in the US in 1996 (US5635517 A). Our research did not identify a matching patent applied for in South Africa.

In South Africa, eight secondary patents on thalidomide and lenalidomide have been granted which, if unchallenged, could prevent the use of generic products in the country until 2026 (71 years since the initial patent on thalidomide was granted in the US and 30 years after the initial lenalidomide patent was granted). Secondary patents granted and upheld in South Africa include patents that were withdrawn in Germany and at the European Patent Office and refused in South Korea.

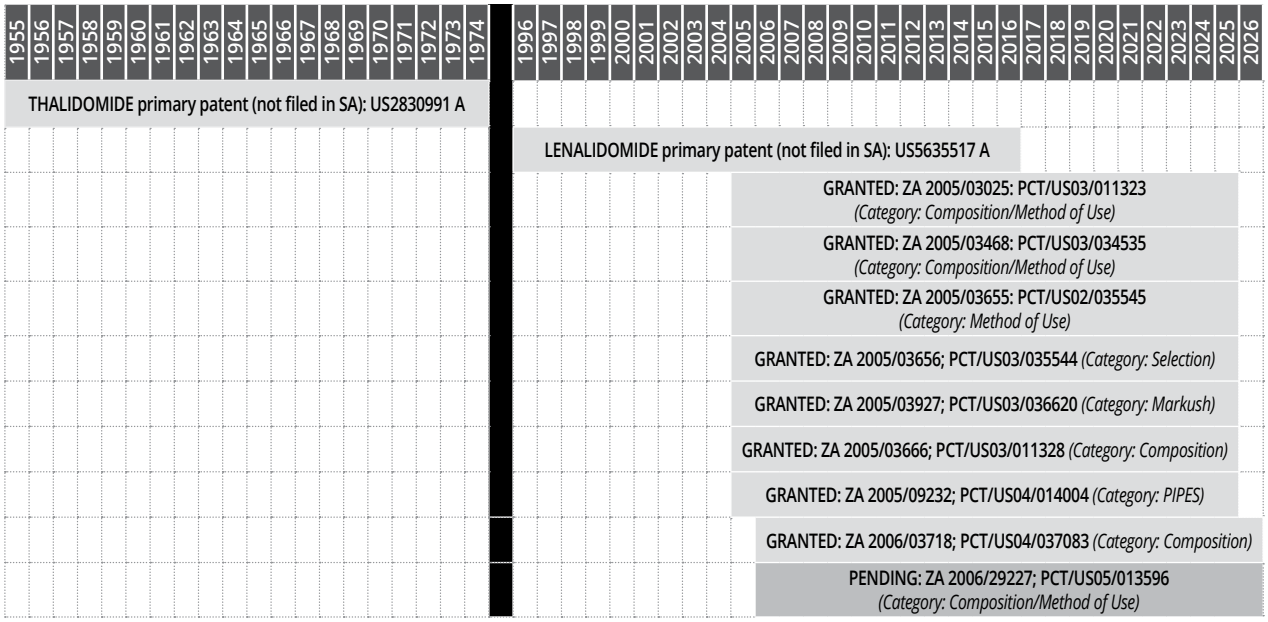
With strong patentability criteria, examination and opposition procedures as proposed in the 2017 draft IP Policy, secondary patents held in South Africa may not have been granted allowing for earlier entry of generic products. Additionally, if South Africa reforms its processes for granting compulsory licenses, compulsory licensing could be used as an expedited mechanism to access more affordable generic thalidomide and lenalidomide in South Africa.

PATENTS GRANTED ON THALIDOMIDE AND LENALIDOMIDE IN SOUTH AFRICA

Patent Title	Patent Holder	CIPC Number	Lodging Date	Expiry Date	Legal Status	PCT Number	Territories where matching patent applications were withdrawn or refused
METHODS OF USING AND COMPOSITIONS COMPRISING IMMUNOMODULATORY COMPOUNDS FOR THE TREATMENT AND MANAGEMENT OF MYELODYSPLASTIC SYNDROMES	CELGENE CORPORATION	2005/03025	14-Apr-2005	14-April-2025	Granted	PCT/ US03/011323	- Refused in South Korea
METHODS OF USING AND COMPOSITIONS COMPRISING SELECTIVE CYTOKINE INHIBITORY DRUGS FOR TREATMENT AND MANAGEMENT OF MACULAR DEGENERATION	CELGENE CORPORATION	2005/03468	29-Apr-2005	29-April-2025	Granted	PCT/ US03/034535	
METHODS AND COMPOSITIONS USING SELECTIVE CYTOKINE INHIBITORY DRUGS FOR TREATMENT AND MANAGEMENT OF CANCERS AND OTHER DISEASES	CELGENE CORPORATION	2005/03655	06-May-2005	06-May-2025	Granted	PCT/ US03/035545	- Withdrawn at the EPO - Refused in South Korea

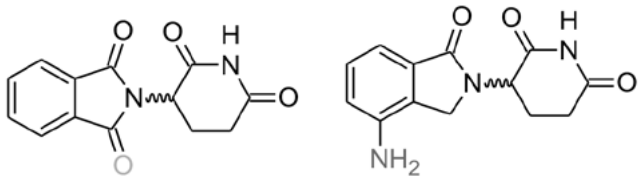
PATENTS GRANTED ON THALIDOMIDE AND LENALIDOMIDE IN SOUTH AFRICA							
Patent Title	**Patent Holder**	**CIPC Number**	**Lodging Date**	**Expiry Date**	**Legal Status**	**PCT Number**	**Territories where matching patent applications were withdrawn or refused**
METHODS FOR TREATMENT AND MANAGEMENT OF BRAIN CANCER USING 1-Oxo-2-(2,6-DIOXOPIPERIDIN-3-YL)-4-METHYLISOINDOLINE	CELGENE CORPORATION	2005/03656	06-May-2005	06-May-2025	Granted	PCT/ US03/035544	- Withdrawn at the EPO
PHARMACEUTICAL COMPOSITIONS AND DOSAGE FORMS OF LENALIDOMIDE	CELGENE CORPORATION	2005/03927	16 May 2005	16 May 2025	Granted	PCT/ US03/036620	
METHODS OF USING AND COMPOSITIONS COMPRISING IMMUNOMUDULATORY COMPOUNDS FOR THE TREATMENT AND MANAGEMENT OF MYELOPROLIFERATIVE DISEASES	CELGENE CORPORATION	2005/03666	06-May-2005	06-May-2025	Granted	PCT/ US03/011328	
METHODS FOR TREATING CANCERS USING POLYMORPHIC FORMS OF 3-(4-AMINO-1,3DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE -2,6-DIONE	CELGENE CORPORATION	2005/09232	15-Nov-2005	15-Nov-2025	Granted	PCT/ US04/014004	- Withdrawn at the EPO - Withdrawn in Russia - Refused in South Korea
METHODS AND COMPOSITIONS USING THALIDOMIDE FOR THE TREATMENT AND MANAGEMENT OF CANCERS AND OTHER DISEASES	CELGENE CORPORATION	2006/03718	10-May-2006	10-May-2026	Granted	PCT/ US04/037083	- Withdrawn at the EPO - Withdrawn in South Korea
METHODS OF USING AND COMPOSITIONS COMPRISING THALIDOMIDE FOR THE TREATMENT AND MANAGEMENT OF PULMONARY HYPERTENSION	CELGENE CORPORATION	2006/29227	06-Nov-2006	06-Nov-2026	Pending	PCT/ US05/013596	- Withdrawn in Germany - Withdrawn at the EPO - Withdrawn in South Korea

TIMELINE OF PATENTS GRANTED ON THALIDOMIDE AND LENALIDOMIDE



RELATIONSHIP BETWEEN THALIDOMIDE AND LENALIDOMIDE

Lenalidomide is a derivative of thalidomide developed following research demonstrating thalidomide's efficacy in treating cancer. The removal of the carbonyl group (=O) and the addition of the amide group (-NH2) resulted in enhanced pharmacological activity and less side effects.



Thalidomide Lenalidomide

3. BORTEZOMIB

BORTEZOMIB PRICE AND AVAILABILITY

Bortezomib is indicated for the treatment of multiple myeloma. At the start of this study, only Janssen's originator product sold under the brand name Velcade was available in South Africa, and patents held by Millennium Pharmaceuticals threatened to inhibit generic use until 2035 if unchallenged (Millennium Pharmaceuticals is owned by Takeda which has a marketing agreement with Janssen for the sale of Bortezomib).

However, in 2017 Accord's generic bortezomib was launched in South Africa resulting in a 50% price reduction for the drug. It is unclear whether Accord launched their product at risk, or has a licensing agreement with Janssen and/or Takeda. A request for clarification has been sent to Accord and any response will be incorporated into later versions of this report.

While the launch of Accord's product led to a large price reduction, the cost of their product is still significantly higher (76%) than bortezomib generics in India where multiple generic products are registered. Bortezomib is currently unavailable in South Africa's public sector and can only be accessed via the private sector.

BORTEZOMIB PRICES

Dosage and formulation	Originator and generic product prices in SA private sector	Originator and generic product prices in SA public sector	Generic prices in Canada (if available)	Generic prices in India (if available)
bortezomib 2mg injection ++	N/A	N/A	N/A	Rs 12,688 (Natco) ZAR 2,579 Rs 13,125 (Dr Reddy) ZAR 2,668 Rs 15,852 (Emcure) ZAR 3,222
bortezomib 3.5mg injection ++	ZAR16,664 (Janssen/ Originator) ZAR 10,994 (Accord/ Generic)	N/A	N/A	Rs 12,500 (Natco) ZAR 2,540 Rs18,552 (Dr Reddy) ZAR 3,771

++ cost per vial

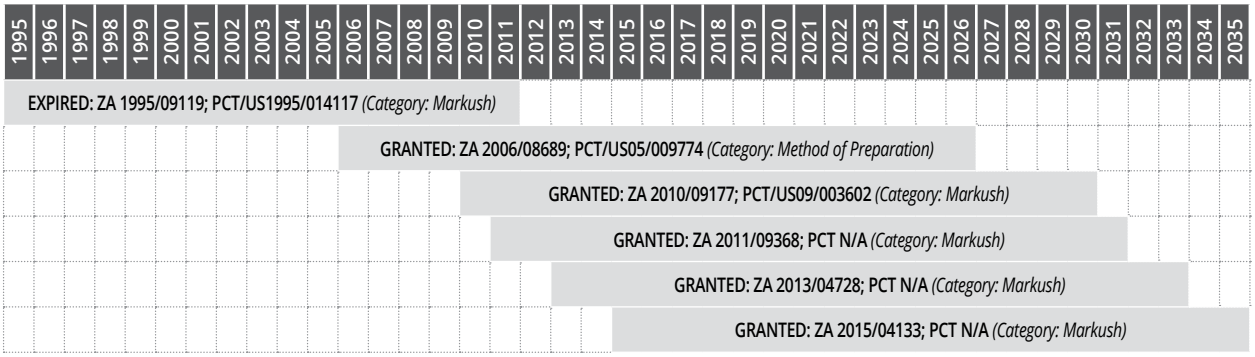
PATENTS GRANTED ON BORTEZOMIB IN SOUTH AFRICA

The earliest patent granted on bortezomib was the patent entitled "Boronic ester and acid compounds, synthesis and uses". This patent was granted in 1994 in the US and 1995 in South Africa. This patent application cited prior applications on boron compounds and boronic acid as prior art, dating back to 1981.

Five secondary patents related to bortezomib were also identified in South Africa lasting until 2035 (40 years after the initial patent was granted). Secondary patents granted in South Africa include patents withdrawn in Germany and refused in South Korea. With strong patentability criteria, examination and opposition procedures as proposed in the 2017 draft IP Policy, secondary patents held in South Africa may not have been granted.

PATENTS GRANTED ON BORTEZOMIB IN SOUTH AFRICA							
Patent Title	**Patent Holder**	**CIPC Number**	**Lodging Date**	**Expiry Date**	**Legal Status**	**PCT Number**	**Territories where matching patent applications were withdrawn or refused**
BORONIC ESTER AND ACID COMPOUNDS, SYNTHESIS AND USES	Millennium Pharmaceuticals	1995/09119	27-Oct-1995	27-Oct -2011	Granted	PCT/ US1995/014117	
SYNTHESIS OF BORONIC ESTER AND ACID COMPOUNDS	Millennium Pharmaceuticals	2006/08689	18-Oct-2006	18-Oct-2026	Granted	PCT/ US05/009774	- Withdrawn in Germany
BORONATE ESTER COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS THEREOF	Millennium Pharmaceuticals	2010/09177	21-Dec-2010	21-Dec -2030	Granted	PCT/ US09/003602	- Refused in South Korea
BORONATE ESTER COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS THEREOF	Millennium Pharmaceuticals	2011/09368	20-Dec-2011	20-Dec -2031	Granted	N/A	
BORONATE ESTER CONPOUNDDS AND PHARMACEUTICAL COMPOSITIONS THEREOF	Millennium Pharmaceuticals	2013/04728	25-Jun-2013	25-Jun-2033	Granted	N/A	
BORONATE ESTER COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS THEREOF	Millennium Pharmaceuticals	2015/04133	08-Jun-2015	8-Jun -2035	Granted	N/A	

TIMELINE OF PATENTS GRANTED ON BORTEZOMIB



4. BENDAMUSTINE

BENDAMUSTINE PRICE AND AVAILABILITY

Bendamustine is recommended as an essential treatment for chronic lymphocytic leukemia and follicular lymphoma by the WHO. In South Africa bendamustine is indicated for the treatment of chronic lymphocytic leukemia, non-Hodgkin's lymphoma, and multiple myeloma – but is not included on South Africa's essential medicines list. Bendamustine is not available in South Africa's public sector and can only be accessed in the private sector.

In South Africa, where only Astellas's originator products are available sold under the brand name Ribomustine, a full course of originator bendamustine cost approximately ZAR 50,184. A typical full-course of bendamustine involves intravenous dosing of 100mg for two days in a row in a 28-day cycle for 6 cycles. By comparison a full course of generic bendamustine in India costs approximately ZAR16,800.

BENDAMUSTINE PRICES

Dosage and formulation	Originator product prices in SA private sector	Originator product prices in SA public sector	Generic prices in Canada (if available)	Generic prices in India (if available)
bendamustine 25mg powder for injection +	ZAR 1,045 (Astellas)	N/A	N/A	N/A
bendamustine 100mg powder for injection ++	ZAR 4,182 (Astellas)	N/A	N/A	Rs 6,416 (Emcure) ZAR 1,304 Rs 6,571 (Cipla) ZAR 1,336 Rs 6,950 (Natco) ZAR 1,413

+ price per 25mg ++ price per 100mg

PATENTS GRANTED ON BENDAMUSTINE IN SOUTH AFRICA

Bendamustine was synthesized in 1963 in East Germany.[38] [39] Following a series of licensing deals and company acquisitions, Cephalon and Astellas acquired the rights to develop and market bendamustine in 2005.[40] Five secondary patents have been granted on bendamustine in South Africa to Cephalon (which markets bendamustine in the US in partnership with Teva) and Astellas. If unchallenged, these patents could prevent the use of generic bendamustine in South Africa until 2032. Patents granted and upheld in South Africa include patents that were withdrawn in Europe and refused in South Korea.

With strong patentability criteria, examination and opposition procedures as proposed in the 2017 draft IP Policy, secondary patents held in South Africa may not have been granted allowing for earlier entry of generic products. Additionally, if South Africa reforms its processes for granting compulsory licenses, then compulsory licensing could be used as an expedited mechanism to access more affordable generic bendamustine in South Africa.

PATENTS GRANTED ON BENDAMUSTINE IN SOUTH AFRICA							
Patent Title	**Patent Holder**	**CIPC Number**	**Lodging Date**	**Expiry Date**	**Legal Status**	**PCT Number**	**Territories where matching patents withdrawn or refused**
BENDAMUSTINE PHARMACEUTICAL COMPOSITIONS FOR LYOPHILISATION	CEPHALON INC	2007/05793	13-Jul-2007	13-Jul-2027	Accepted	PCT/ US06/001308	- Revoked by the EPO
SOLID DOSAGE FORMS OF BENDAMUSTINE	ASTELLAS DEUTSCHLAND GMBH	2011/03790	24-May-2011	24-May-2031	Granted	PCT/ EP09/008639	
ORAL DOSAGE FORMS OF BENDAMUSTINE	ASTELLAS DEUTSCHLAND GMBH	2011/03791	24-May-2011	24-May-2031	Granted	PCT/ EP09/008857	
NOVEL FORMS OF BENDAMUSTINE FREE BASE	CEPHALON INC	2011/05099	11-Jul-2011	11-Jul-2031	Granted	PCT/ US10/020992	- Withdrawn at the EPO - Refused in South Korea
ORAL DOSAGE FORMS OF BENDAMUSTINE AND THERAPEUTIC USE THEREOF	ASTELLAS DEUTSCHLAND GMBH	2012/08822	22-Nov-2012	22-Nov-2032	Granted	PCT/ EP11/002763	Under examination at the EPO
ORAL DOSAGE FORMS OF BENDAMUSTINE	ASTELLAS DEUTSCHLAND GMBH	2012/08823	22-Nov-2012	22-Nov-2032	Granted	PCT/ EP11/002764	Under examination at the EPO

TIMELINE OF PATENTS GRANTED ON BENDAMUSTINE

5. DAUNORUBICIN

DAUNORUBICIN PRICE AND AVAILABILITY

Daunorubicin is recommended as an essential treatment for acute lymphoblastic leukemia, acute myelogenous leukemia and acute promyelocytic leukemia by the WHO. In South Africa daunorubicin is indicated for acute myeloblastic and lymphoblastic leukemia – but it is not recommended as an essential treatment.

Only Pfizer's originator version of daunorubicin is available in South Africa sold under the brand name Daunoblastin. Pfizer's Daunoblastin is available in both South Africa's public and private sectors. In the public sector, Pfizer sells daunorubicin at comparable prices to generics available in India. In the private sector, Pfizer's daunorubicin is more than 6 times more expensive than equivalent generic products in India.

DAUNORUBICIN PRICES

Dosage and formulation	Originator product prices in SA private sector	Originator product prices in SA public sector	Generic prices in Canada (if available)	Generic prices in India (if available)
daunorubicin 20 mg powder for injection +	ZAR 515.33 (Pfizer)	R92.64 (Pfizer)	N/A	Rs 399 (Cipla) ZAR 81.09 Rs 400 (VHB) ZAR 81.30

+ price per 20mg

PATENTS GRANTED ON DAUNORUBICIN IN SOUTH AFRICA

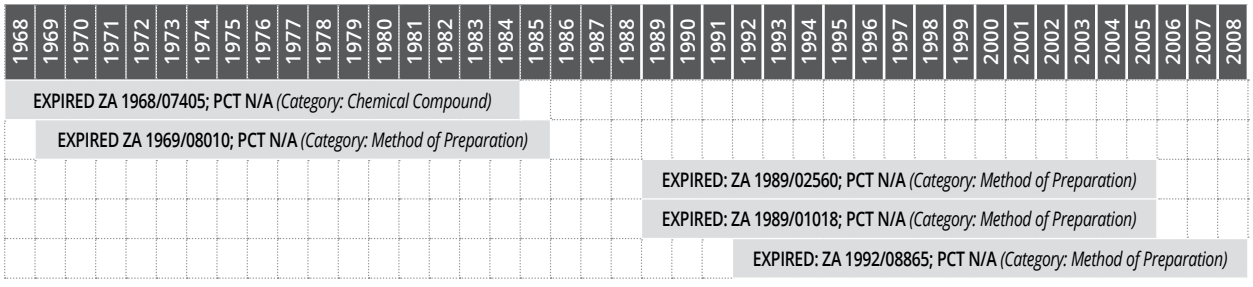
The primary patent on daunorubicin was granted in 1969. Subsequently four secondary patents were granted lasting until 2008 (40 years after the initial patent was granted). However, as all identified patents are expired, it is unclear why generic daunorubicin products remain unavailable in the country. Further communication should be pursued with generic producers to gain greater insight regarding why generic products are unavailable. Barriers to generic entry may include: 1. ongoing patent barriers that were not identified, 2. regulatory delays and/or 3. lack of interest by generic producers to register and market their products in South Africa.

PATENTS GRANTED ON DAUNORUBICIN IN SOUTH AFRICA

Patent Title	Patent Holder	CIPC Number	Lodging Date	Expiry Date	Legal Status	PCT Number
NEW PROCESS THE PREPARATION DAUNORUBICIN	RHONE-PAULENC SA	1968/07405	14-Nov-1968	14-Nov-1984	Expired	N/A
NEW PROCESS FOR THE PREPARATION OF DAUNORUBICIN	RHONE-PAULENC SA	1969/08010	17-Nov-1969	17-Nov-1985	Expired	N/A
PROCESS FOR PREPARING 4-DEMETHOXYDAUNOMYCINONE	PHARMACIA & UPJOHN SPA	1989/02560	07-Apr-1989	07-April-2005	Expired	N/A
PROCESS FOR THE PREPARATION OF 4-DEMETHOXYDAUNOMYCINONE, THE AGLYCONE OF 4-DEMETHOXY-DAUNORUBICIN	PHARMACIA & UPJOHN	1989/01018	09-Feb-1989	09-Feb-2005	Expired	N/A
PROCESS FOR PREPARING DAUNORUBICIN	PHARMACIA UPJOHN*	1992/08865	17-Nov-1992	17-Nov-2008	Expired	N/A

**Merged with Pfizer in 2003. Pharmacia corp and Gilead relationship: http://www.gilead.com/news/press-releases/2001/11/osi-pharmaceuticals-acquires-oncology-assets-from-gilead-sciences*

TIMELINE OF PATENTS GRANTED ON DAUNORUBICIN IN SOUTH AFRICA



6. DACARBAZINE

DACARBAZINE PRICE AND AVAILABILITY

Dacarbazine is recommended as an essential medicine for Hodgkin lymphoma by the WHO. In South Africa dacarbazine is indicated for treatment of Hodgkin lymphoma, malignant melanoma, and metastatic sarcoma – but it is not recommended as an essential medicine. Currently Bayer is the only supplier of dacarbazine in South Africa. Aspen Pharmacare received registration for generic dacarbazine in South Africa in 2011 but is not marketing the treatment.[41] During 2017, Section 21 authorisation was granted for importation of emergency stock of Medac's dacarbazine by Equity Pharmaceuticals.[42]

Currently only Bayer's originator dacarbazine is available in South Africa under the brand name Dtic. The cost of a 200mg vial of dacarbazine in South Africa's private sector is ZAR 203.50 – which is more than double the cost of equivalent generic products in India. Dacarbazine is not procured nationally for use in the public sector.

DACARBAZINE PRICES

Dosage and formulation	Originator product prices in SA private sector	Originator product prices in SA public sector	Generic prices in Canada (if available)	Generic prices in India (if available)
dacarbazine 200 mg vial +	ZAR 203.50* (Bayer)	N/A	N/A	Rs 312 (Intas) ZAR 63.41 Rs 433 (Celon) ZAR 88.01 Rs 476 (Cipla) ZAR 96.75

*+ price per vial * Note: this product has a high dispensing fee*

PATENTS GRANTED ON DACARBAZINE IN SOUTH AFRICA

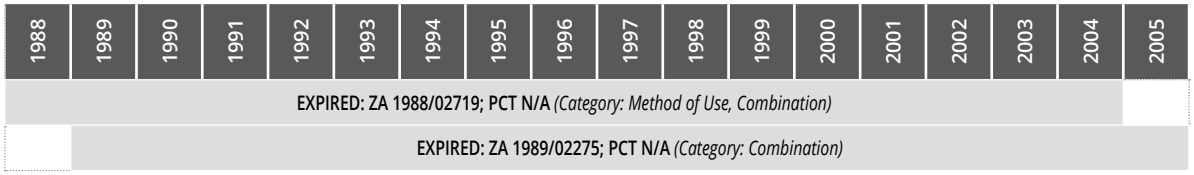
Dacarbazine was synthesized in1961.[43] The earliest identified related patent was filed in the US in 1967 (US 3649613). An equivalent patent was not identified in South Africa. Two secondary patents were filed on dacarbazine in South Africa in 1988 and 1989 – both of which have expired.

As identified patents have expired, it is unclear why generic products remain unavailable in the country. Further communication should be pursued with generic producers to gain greater insight regarding why generic products are not available. Barriers to generic entry may include: 1. ongoing patent barriers that were not identified, 2. regulatory delays and/or 3. lack of interest by generic producers to register and market their products in South Africa.

PATENTS GRANTED ON DACARBAZINE IN SOUTH AFRICA

Patent Title	Patent Holder	CIPC Number	Lodging Date	Expiry Date	Legal Status	PCT Number
USE OF ODC INHIBITORS, DACARBAZINE, AND INTERFERON IN THE TREATMENT OF MALIGNANT MELANOMA	MERRELL DOW PHARMACEUTICALS INC	1988/02719	18-Apr-1988	18-Apr-2004	Expired	N/A
COMBINATION THERAPY OF IL-2 AND DTIC FOR THE TREATMENT OF MELANOMA	CETUS CORPORATION	1989/02275	28-Mar-1989	28-Mar-2005	Expired	N/A

TIMELINE OF PATENTS GRANTED ON DACARBAZINE



7. DASATINIB

DASATINIB PRICE AND AVAILABILITY

Dasatinib is recommended as an essential treatment for imatinib-resistant chronic myeloid leukemia by the WHO. In South Africa, dasatinib is recommended for treatment of chronic myeloid leukemia (CML) in patients that are resistant or intolerant of imatinib. Only Bristol Myers-Squibb's originator dasatinib is available in South Africa sold under the brand name Sprycel, costing around ZAR22,000 per month in the private sector for an average course of treatment. Dasatinib is typically taken at 100mg daily for as long as clinical benefit is provided. Dasatinib is not procured nationally for public sector use.

No generic dasatinib products were identified in South Africa, India, the US, EU, or Canada. However, health economists at the University of Liverpool have estimated that in the absence of intellectual property monopolies dasatinib could be produced profitably for £9 (ZAR 150) per month.[44]

DASATINIB PRICES				
Dosage and formulation	Originator product prices in SA private sector	Originator product prices in SA public sector	Generic prices in Canada (if available)	Generic prices in India (if available)
dasatinib 100mg tablet+	ZAR 723.57 (BMS)	N/A	N/A	N/A

+ price per tablet

PATENTS GRANTED ON DASATINIB IN SOUTH AFRICA

Patent monopolies remain a barrier to generic entry globally. Efforts in India to secure a compulsory license to allow for generic production of dasatanib to date have been unsuccessful.[45]

The initial patent on dasatinib's method of production was filed in South Africa in 2006 under the title "Process for preparing 2-Aminothiazole-5-Aromatic Carboxamides as kinase inhibitors". Dasatinib also enjoys earlier protections broadly granted on tyrosine kinase inhibitors in South Africa. Patents related to dasatinib in South Africa include patents withdrawn in the Philippines and Germany, refused in South Korea and invalidated in Europe. With strong patentability criteria, examination and opposition procedures as proposed in the 2017 draft IP Policy, it is likely that many of these secondary patents would not have been granted allowing for earlier entry of generic dasatinib.

PATENTS GRANTED ON DASATINIB IN SOUTH AFRICA							
Patent Title	Patent Holder	CIPC Number	Lodging Date	Expiry Date	Legal Status	PCT Number	Territories where matching patents withdrawn or refused
CYCLIC PROTEIN TYROSINE KINASE INHIBITORS	BRISTOL-MYERS SQUIBB HOLDINGS IRELAND	2001/07204	30-Aug-2001	30-Aug-2021	Granted	PCT/US00/009753	- Invalidated in Europe (EP 1169038[46]
CYCLIC PROTEIN TYROSINE KINASE INHIBITORS	BRISTOL-MYERS SQUIBB HOLDINGS IRELAND	2005/07718	23-Sep-2005	23-Sep-2025	Granted	PCT/US04/008827	- Withdrawn in the Philippines
PROCESS FOR PREPARING 2-AMINOTHIAZOLE-5-AROMATIC CARBOXAMIDES AS KINASE INHIBITORS	BRISTOL-MYERS SQUIBB HOLDINGS IRELAND	2006/06242	27-Jul-2006	27-Jul-2026	Granted	PCT/US05/003728	- Withdrawn in Germany - Withdrawn in the Philippines - Refused in South Korea

Indian patent 203937 was upheld following request for compulsory license and litigation by BDR[47]

TIMELINE OF PATENTS GRANTED ON DASATINIB

8. NILOTINIB

NILOTINIB PRICE AND AVAILABILITY

Nilotinib is recommended as an essential treatment for chronic myeloid leukemia by the World Health Organisation and in South Africa. In South Africa, only Novartis originator product is available sold under the brand name Tasigna. Tasigna is available in both South Africa's public and private sectors.

Imatinib resistant or intolerant patients are generally given 400mg of nilotinib twice daily. In the private sector, a month of nilotinib treatment costs around ZAR 29,060. In the public sector, a month of nilotinib is sold by Novartis at significantly lower prices of around ZAR 2,064. No generic nilotinib products were identified in South Africa, India, Canada, the US, or EU.

NILOTINIB PRICES

Dosage and formulation	Originator product prices in SA private sector	Originator product prices in SA public sector	Generic prices in Canada (if available)	Generic prices in India (if available)
nilotinib 150mg capsule	ZAR 182.07 (Novartis)	N/A	N/A	N/A
nilotinib 200mg capsule	ZAR 242.76 (Novartis)	ZAR 17.20 (Novartis)	N/A	N/A

+ price per capsule

PATENTS GRANTED ON NILOTINIB IN SOUTH AFRICA

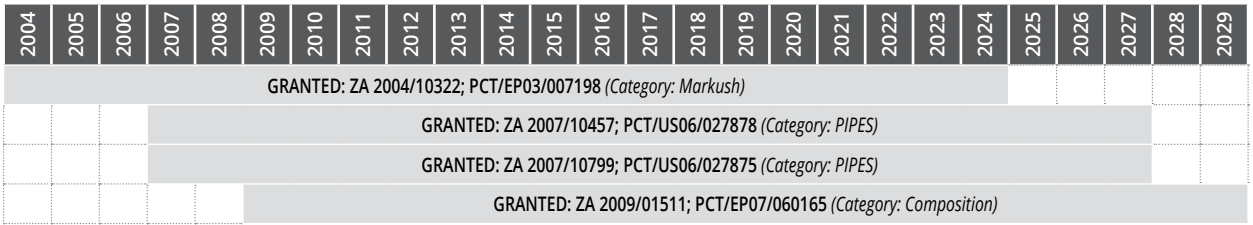
Building on earlier work related to the activity of protein kinase BCR-ABL in patients with chronic myeloid leukemia and the development of tyrosine kinase inhibitors for the treatment thereof, Nilotinib was designed to treat imatinib resistant CML.[48] The development of nilotinib was first reported in 2006.[49]

Four patents related to nilotinib were granted in South Africa between 2004 and 2009. If unchallenged, these patents could prevent the use of generic nilotinib products in South Africa until 2029. Patents granted and upheld in South Africa include patents that were withdrawn in Germany and the EPO and refused in South Korea. With strong patentability criteria, examination and opposition procedures as proposed in the 2017 draft IP Policy, it is likely that many of these secondary patents would not have been granted allowing for earlier entry of generic nilotinib.

PATENTS GRANTED ON NILOTINIB IN SOUTH AFRICA

Patent Title	Patent Holder	CIPC Number	Lodging Date	Expiry Date	Legal Status	PCT Number	Territories where matching patents withdrawn or refused
INHIBITORS OF TYROSINE KINASES	NOVARTIS AG	2004/10322	22-Dec-2004	22-Dec-2024	Granted	PCT/ EP03/007198	
SALTS OF 4-METHYL-N-[3-(4-METHYL-IMIDAZOL-1-YL)-5-TRIFLUOROMETHYL-PHENYL]-3-(4-PYRIDIN-3-YL-PYRIDIN-3-YL-PYRIMIDIN-2-YLAMINO)-BENZAMIDE	NOVARTIS AG	2007/10457	03-Dec-2007	03-Dec-2027	Granted	PCT/ US06/027878	- Withdrawn in Germany - Refused in South Korea
CRYSTALLINE FORMS OF 4-METHYL-N-[3-(4-METHYL-IMIDAZOL-1-YL)-5-TRIFLUOROMETHYLPHENYL]-3-(4-[PYRIDIN-3-YL-PYRIMIDIN-2-YLAMINO)-BENZAMIDE	NOVARTIS AG	2007/10799	12-Dec-2007	12-Dec-2027	Granted	PCT/ US06/027875	- Withdrawn in Germany - Withdrawn at the EPO - Refused in South Korea
PHARMACEUTICAL COMPOSITIONS COMPRISING NILOTINIB OR ITS SALT	NOVARTIS AG	2009/01511	03-Mar-2009	03-Mar-2029	Granted	PCT/ EP07/060165	

TIMELINE OF PATENTS GRANTED ON NILOTINIB



9. RITUXIMAB

RITUXIMAB PRICE AND AVAILABILITY

Rituximab is recommended by the WHO as an essential treatment for diffuse large B-cell lymphoma, chronic lymphocytic leukemia, and follicular lymphoma. In South Africa, rituximab is indicated for the treatment of D-cell non-Hodgkin lymphomas and follicular lymphoma, but only recommended as an essential treatment for the first indication.

In South Africa only Roche's originator product is available sold under the brand name Mabthera. During 2016, rituximab was the 7th highest driver of medicine expenditure by medical insurers in South Africa. A single 500mg vial costs ZAR 16,822 in the private sector. In the public sector, Roche markets Mabthera at a lower price of ZAR 7,950 per 500mg vial.

Currently the cost of biosimilar rituximab products in India are similar to the cost of rituximab in South Africa's public sector – although it can be anticipated that the cost of biosimilar rituximab products will decline as their use increases globally as biosimilar products receive pre-qualification by the WHO[50] and registration approval by stringent regulatory authorities[51,52].

RITUXIMAB PRICES

Dosage and formulation	Originator product prices in SA private sector	Originator product prices in SA public sector	Generic prices in Canada (if available)	Generic prices in India (if available)
rituximab 100mg/10ml infusion ++	ZAR 3,365 (Roche)	ZAR 1,590 (Roche)	N/A	Rs 5000 (Hetero) ZAR 1,016 Rs 7583 (Emcure) ZAR 1,541
rituximab 500mg/50ml infusion ++	ZAR 16,822 (Roche)	ZAR 7,950 (Roche)		Rs 25,000 (Hetero) ZAR 5,081 Rs 36,946 (Torrent) ZAR 7,509 Rs 37,917 (Emcure) ZAR 7,707

PATENTS GRANTED ON RITUXIMAB IN SOUTH AFRICA

The discovery of antigen CD20 expressed in certain cancers led to the development of anti-CD20 based therapies for the treatment of certain cancers.[53] The earliest identified patent for anti-CD20 therapy was granted to Xoma Corporation in South Africa in 1988. Subsequently, five secondary patents have been granted that could extend Roche's monopoly on the medicine until 2030 – 42 years after the original patent was granted – if unchallenged. Pending patent applications could further extend Roche's monopoly another 6 years if granted.

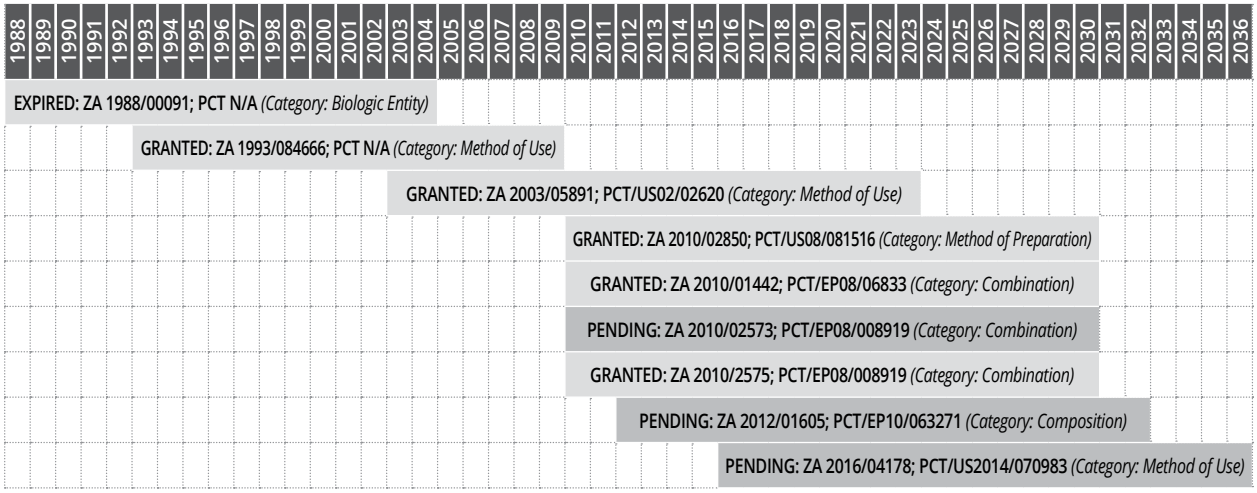
Patents granted, upheld and pending on rituxumab in South Africa include patents that were withdrawn in Europe and the Philippines and refused in South Korea. With strong patentability criteria, examination and opposition procedures as proposed in the 2017 draft IP Policy, it is likely that many of these secondary patents in South Africa would not have been granted allowing for earlier entry of biosimilar products.

PATENTS GRANTED ON RITUXIMAB IN SOUTH AFRICA							
Patent Title	**Patent Holder**	**CIPC Number**	**Lodging Date**	**Expiry Date**	**Legal Status**	**PCT Number**	**Territories where matching patents withdrawn or refused**
CHIMERIC ANTIBODY WITH SPECIFICITY TO HUMAN B CELL SURFACE ANTIGEN	XOMA CORPORATION	1988/00091	07-Jan-1988	07-Jan-2004	Granted	N/A	
THERAPEUTIC APPLICATION OF CHIMERIC AND RADIOLABELED ANTIBODIES TO HUMAN B LYMPHOCYTE RESTRICTED DIFFERENTIATION ANTIGEN FOR TREATMENT OF B CELL LYMPHOMA	BIOGEN IDEC INC*	1993/08466	12-Nov-1993	12-Nov-2009	Granted	N/A	
USE OF CD23 ANTAGONISTS FOR THE TREATMENT OF NEOPLASTIC DISORDERS	BIOGEN IDEC INC	2003/05891	30-Jul-2003	30-Jul-2023	Granted	PCT/ US02/02620	- Withdrawn at the EPO - Refused in South Korea
ANTIBODY PURIFICATION BY CATION EXCHANGE CHROMATOGRAPHY	GENENTECH INC**	2010/02850	22-Apr-2010	22-Apr-2030	Granted	PCT/ US08/081516	
COMBINATION THERAPY WITH TYPE I AND TYPE II ANTI-CD20 ANTIBODIES	ROCHE GLYCART AG	2010/01442	26-Feb-2010	26-Feb-2030	Granted	PCT/ EP08/006833	- Withdrawn in the Philippines
COMBINATION THEPARY OF A TYPE II ANTI-CD20 ANTIBODY WITH AN ANTI-BCL-2 ACTIVE AGENT	ROCHE GLYCART AG	2010/02573	13-Apr-2010	13-Apr-2030	Pending	PCT/ EP08/008635	- Withdrawn at the EPO
COMBINATION THERAPY OF A TYPE II ANTI-CD20 ANTIBODY WITH A PROTEASOME INHIBITOR	ROCHE GLYCART AG	2010/02575	13-Apr-2010	13-Apr-2030	Granted	PCT/ EP08/008919	- Withdrawn in the Philippines
HIGHLY CONCENTRATED PHARMACEUTICAL FORMULATIONS COMPRISING ANTI-CD20 ANTIBODY	HOFFMANN-LA ROCHE AG	2012/01605	02-Mar-2012	02-Mar-2032	Pending	PCT/ EP10/063271	
METHODS OF TREATING CANCER USING PD-1 AXIS BINDING ANTAGONISTS AND AN ANTI-CD20 ANTIBODY	GENENTECH, INC	2016/04178	21-Jun-2016	21-Jun-2036	Pending	PCT/ US2014/070983	- Examination in progress at the EPO

** Biogen and Genentech have a profit share arrangement related to rituximab*[54]

*** Genentech is a subsidiary of Roche*

TIMELINE OF PATENTS GRANTED ON RITUXIMAB



10+11. ASPARAGINASE AND PEGASPARGASE

ASPARAGINASE AND PEGASPARGASE PRICE AND AVAILABILITY

Asparaginase is recommended by the WHO as an essential treatment for acute lymphoblastic leukemia. In South Africa, it is not listed as an essential treatment, but indicated for the treatment of acute lymphoblastic leukemia. Only Bodene's originator asparaginase product is available in South Africa, sold under the brand name Laspar. Pegaspargase, the PEGylated form of asparagine marketed under the brand name Oncaspar, is not available in South Africa in originator or generic form.

Bodene's asparaginase is sold in South Africa's private sector at ZAR 1,327 per 10000 iu injection, but is unavailable in the public sector. Generic asparaginase is available at lower prices in India ranging between ZAR 188 and ZAR 499 per 10000 iu injection.

ASPARAGINASE PRICES				
Dosage and formulation	**Originator product prices in SA private sector**	**Originator product prices in SA public sector**	**Generic prices in Canada (if available)**	**Generic prices in India (if available)**
asparaginase 5000 iu injection	N/A	N/A	N/A	Rs 567 (Sun) ZAR 115.24 Rs 975 (Celon) ZAR 198.17 Rs 1,184 (Biochem) ZAR 240.65
asparaginase 10000 iu injection +	ZAR 1,327 (Bodene)	N/A	N/A	Rs 923 (Sun) ZAR 187.60 Rs 1,500 (Celon) ZAR 304.88 Rs 2,448 (Biochem) ZAR 497.56

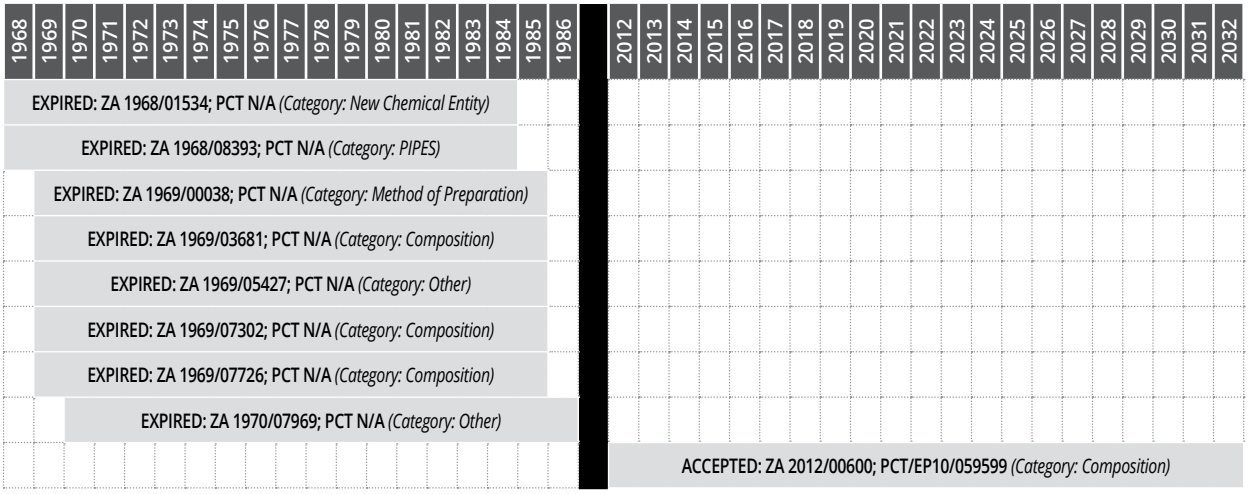
PEGASPARGASE PRICES				
Dosage and formulation	**Originator product prices in SA private sector**	**Originator product prices in SA public sector**	**Generic prices in Canada (if available)**	**Generic prices in India (if available)**
N/A	N/A	N/A	N/A	N/A

PATENTS GRANTED ON ASPARAGINASE AND PEGASPARGASE IN SOUTH AFRICA

The primary patent on the synthesis of asparaginase was filed in South Africa in 1968. Seven secondary patents were subsequently granted on asparaginase to Bayer and Eli Lilly, all of which have expired. An additional secondary patent was granted in 2012 on PEGylateed aparaginase to Alize Pharma. Alize Pharma was acquired by Jazz Pharmaceuticals[55] the sole supplier of asparaginase in the US and Canada. However, no relationship was identified between Bodene (the sole supplier of asparaginase in South Africa) and Alize Pharma.

PATENTS GRANTED ON ASPARAGINASE AND PEGASPARGASE IN SOUTH AFRICA						
Patent Title	**Patent Holder**	**CIPC Number**	**Lodging Date**	**Expiry Date**	**Legal Status**	**PCT Number**
SYNTHESIS OF L ASPARAGINASE	E R SQUIBB AND SONS INC	1968/01534	11-Mar-1968	11-Mar-1984	Expired	N/A
PROCESS FOR THE ENRICHMENT OF ASPARAGINASE AND CRYSTALLINE LASPARAGINASE	FARBENFABRIKEN BAYER A.G. LEVERKUSEN	1968/08393	20-Dec-1968	20-Dec-1984	Expired	N/A
Process for the extraction of l-asparaginase	FARBENFABRIKEN BAYER AG LEVERKUSEN	1969/00038	03-Jan-1969	03-Jan-1985	Expired	N/A
PROCESS FOR THE STABILIZATION AND PURIFICATION OF L- ASPARAGINASE	FARBENFABRIKEN BAYER AG LEVERKUSEN	1969/03681	23-May-1969	23-May-1985	Expired	N/A
IMPROVED METHOC FOR FERMENTING E. COLI IN A NUTRIENT MEDIUM TO OBTAIN L-ASPARAGINASE	ELI LILLY & COMPANY	1969/05427	29-Jul-1969	29-Jul-1985	Expired	N/A
PARTIALLY DEAMUNATED L-ASPARAGINASE AND PROCESS FOR PREPARING SAME.	FARBENFABRIKEN BAYER AG LEVERKUSEN	1969/07302	16-Oct-1969	16-Oct-1985	Expired	N/A
A CRYSTALLINE COMBINATION OF L-ASPARAGINASE AND A METAL OR METALLOID ION AND METHOD FOR PREPARING THE SAME	ELI LILLY AND COMPANY	1969/07726	04-Nov-1969	04-Nov-1985	Expired	N/A
AZO-L-ASPARAGINASES	FARBENFABRIKEN BAYER AG	1970/07969	24-Nov-1970	24-Nov-1986	Expired	N/A
PEGYLATED L-ASPARAGINASE	ALIZE PHARMA II *	2012/00600	25-Jan-2012	25 Jan 2032	Accepted	PCT/ EP10/059599

TIMELINE OF PATENTS GRANTED ON ASPARAGINASE AND PEGASPARGASE

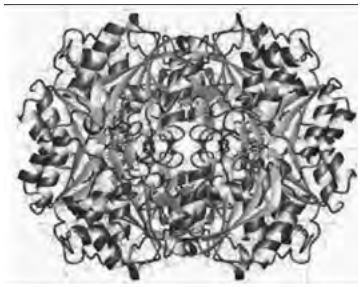
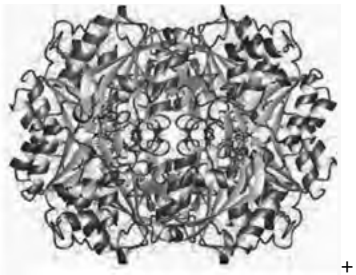
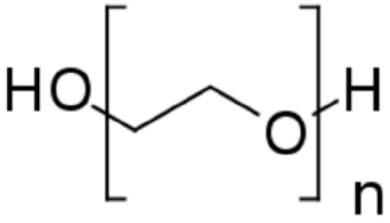


RELATIONSHIP BETWEEN ASPARAGINASE AND PEGASPARGASE

Asparaginase and pegaspargase are both enzymes that break down the amino acid asparagine to ammonia and L-aspartic acid. The amino acid, asparagine, is necessary for the cancer cell to make its DNA. However, the cancer cell is unable to manufacture the amino acid and must get it from circulation (hence ascribed the label "non-essential". Essential amino acids are amino acids that the cell can make itself). Asparagine is an essential amino acid to human cells and so the activity of the enzyme only disadvantages the tumour cell as it is unable to acquire asparagine from circulation.

Pegaspargase differs from asparagine in that it is the PEGylated form of asparagine. PEGylation is the addition of a long chain polymer of poly-ethylene glycol (PEG). This results in the increased solubility of the molecule to which PEG is attached, allowing it to stay in systemic circulation. PEG also masks the molecule to which it is attached from the host's immune system, thus decreasing the molecule's immunogenicity, and it also prolongs circulatory time by decreasing renal clearance.

Structure:

Asparaginase	Pegaspargase
	 + 

12. ERLOTINIB

ERLOTINIB PRICE AND AVAILABILITY

Erlotinib is indicated for locally advanced or metastatic adenocarcinoma of the lung. Erlotinib is not currently recommended as an essential medicine by the WHO, although the Union for International Cancer Control has motivated for its inclusion as an essential treatment for non-small cell lung cancer.[56]

In South Africa, only Roche's originator erlotinib is available sold under the brand name Tarceva. For the treatment of non-small cell lung cancer, Tarceva is generally given daily at 150 mg for as long as clinical benefit is provided. In South Africa, a year of Tarceva at 150 mg per day cost ZAR 314,955 in the private sector. Equivalent generic products are available in India for ZAR 29,565 per year. Tarceva is not available in South Africa's public sector.

ERLOTINIB PRICES				
Dosage and formulation	**Originator product prices in SA private sector**	**Originator product prices in SA public sector**	**Generic prices in Canada (if available)**	**Generic prices in India (if available)**
erlotinib 25mg tab	ZAR 230.10 (Roche)	N/A	CA$ 11.86 (Teva) ZAR 117.65	N/A
erlotinib 100mg tab	ZAR 736.13 (Roche)	N/A	CA$ 47.47 (Teva, Pharmascience) ZAR 470.90	Rs 317.14 (Natco) ZAR 64.43 Rs 625.58 (Glenmark) ZAR 127.24
erlotinib 150mg tab	ZAR 862.89 (Roche)	N/A	CA$ 71.20 (Teva, Pharmascience) ZAR 706.30	Rs 396.67 (Natco) ZAR 80.69 Rs 1019 (Glenmark) ZAR 207.11

+ price per tab

PATENTS GRANTED ON ERLOTINIB IN SOUTH AFRICA

While the 'primary' chemical compound patent on erlotinib was accepted in South Africa in 1999, the drug also benefits from earlier protection accepted on quinzalone derivatives granted in 1996. Subsequently, two additional secondary patents were granted in 2002 and 2005 extending monopoly protection on this medicine until 2025. The 2002 patent which remains in place in South Africa was rejected in India following opposition and litigated against and settled out of court in the United States. An additional pending patent could further extend Roche's monopoly protection on Tarceva in South Africa until 2033 – 37 years after the earliest identified patent was granted.

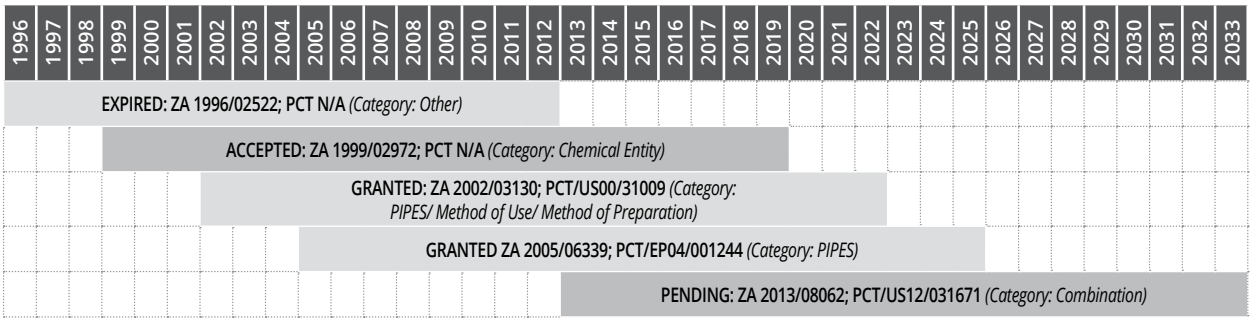
With strong patentability criteria, examination and opposition procedures as proposed in the 2017 draft IP Policy, secondary patents held on erlotinib in South Africa may not have been granted allowing for earlier generic entry. Additionally, if South Africa reforms its processes for granting compulsory licenses, then compulsory licensing could be used as an expedited mechanism to access more affordable generic erlotinib in the country.

Patent Title	Patent Holder	CIPC Number	Lodging Date	Expiry Date	Legal Status	PCT Number	Territories where matching patents withdrawn or refused
QUINAZOLINE DERIVATIVES*	PFRIZER PRODUCTS INCAND OSI PHARMACEUTICALS INC	1996/02522	29-Mar-1996	29-Mar-2012	Granted	N/A	
N 3 ETHYNYLPHENYLAMINO 6 7 BIS 2 METHOXYETHOXY 4 QUINAZOLINAMINE MESYLATE ANHYDRATE AND MONOHYDRATE	OSI PHARMACEUTICALS INC**	1999/02972	28-Apr-1999	28-Apr-2019	Accepted		
STABLE POLYMORPH OF N-(3-ETHYNYLPHENYLAMINO)-6,7-BIS(2-METHOXYETHOXY)-4-QUINAZOLINAMINE HYDROCHLORIDE METHODS OF PRODUCTION AND PHARMACEUTICAL USES THEREOF	OSI PHARMACEUTICALS, LLC	2002/03130	19-Apr-2002	19-Apr-2022	Granted	PCT/US00/31009	- Litigated against in US and settled out of court[57,58] - Rejected in India following opposition[59]
POLYMORPH OF [6,7-BIS(2-METHOXY-ETHOXY)-QUINAZOLIN-4-YL}-(3e)	HOFFMANN-LA ROCHE AG	2005/06339	08-Aug-2005	08-Aug-2025	Granted	PCT/EP04/001244	
COMBINATIONS OF AKT INHIBITOR COMPOUNDS AND ERLOTINIB, AND METHODS OF USE	GENENTECH INC	2013/08062	29-Oct-2013	29-Oct-2033	Pending	PCT/US12/031671	- Withdrawn at the EPO

** Multiple other granted patents related to quinazoline derivates also identified*

*** OSI Pharmaceuticals, Roche and Genentech have a profit share arrangement related to Tarceva*[62]

TIMELINE OF PATENTS GRANTED ON ERLOTINIB



13. CRIZOTINIB

CRIZOTINIB PRICE AND AVAILABILITY

Crizotinib is not registered in South Africa. However, in the US where crizotinib was first approved by the FDA in 2011, it is indicated for the treatment of anaplastic lymphoma kinase (ALK)-positive tumours and metastatic non-small cell lung cancer.

Given that data on pending applications for medicine registration are not publicly available, it is unclear whether Pfizer has submitted an application for registration of crizotinib which it markets under the brand name Xalkori.

No generic crizotinib products are currently available in India, South Africa, the US, Canada, or the EU.

CRIZOTINIB PRICES				
Dosage and formulation	**Originator product prices in SA private sector**	**Originator product prices in SA public sector**	**Generic prices in Canada (if available)**	**Generic prices in India (if available)**
N/A	N/A	N/A	N/A	N/A

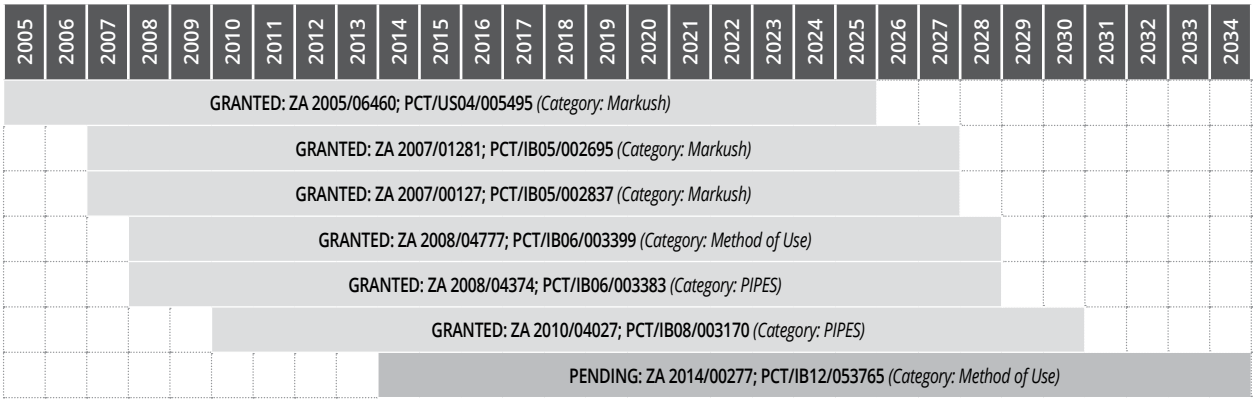
PATENTS GRANTED ON CRIZOTINIB IN SOUTH AFRICA

Crizotinib was initially patented by Sugen Inc in 2005. Sugen Inc was subsequently acquired by Pharmacia, which was then acquired by Pfizer. Five additional granted secondary patents, as well as one pending secondary patent, were identified that could extend Pfizer's monopoly on crizotinib until 2034 – 29 years after the earliest identified patent was granted.

With strong patentability criteria, examination and opposition procedures as proposed in the 2017 draft IP Policy, it is likely that many of these secondary patents on crizotinib would not have been granted allowing for earlier generic entry.

PATENTS GRANTED ON CRIZOTINIB IN SOUTH AFRICA							
Patent Title	**Patent Holder**	**CIPC Number**	**Lodging Date**	**Expiry Date**	**Legal Status**	**PCT Number**	**Territories where matching patents withdrawn or refused**
AMINOHETEROARYL COMPOUNDS AS PROTEIN KINASE INHIBITORS	SUGEN INC.	2005/06460	12-Aug-2005	12-Aug-2025	Granted	PCT/ US04/005495	
PYRAZOLE-SUBSTITUTED AMINOHETEROARYL COMPOUNDS AS PROTEIN KINASE INHIBITORS	PFIZER INC.	2007/01281	13-Feb-2007	13-Feb-2027	Granted	PCT/ IB05/002695	
ENANTIOMERICALLY PURE AMINOHETEROARYL COMPOUNDS AS PROTEIN KINASE INHIBITORS	PFIZER INC.	2007/00127	04-Jan-2007	04-Jan-2027	Granted	PCT/ IB05/002837	
METHOD OF TREATING ABNORMAL CELL GROWTH	PFIZER INC.	2008/04777	02-Jun-2008	02-Jun-2028	Granted	PCT/ IB06/003399	- Withdrawn in Germany - Withdrawn at the EPO
POLYMORPHS OF A C-MET/HGFR INHIBITOR	PFIZER INC.	2008/04374	21-May-2008	21-May-2028	Granted	PCT/ IB06/003383	- Withdrawn in Germany
POLYMORPHS OF A C-MET/HGFR INHIBITOR	PFIZER INC	2010/04027	04-Jun-2010	04-Jun-2030	Granted	PCT/ IB08/003170	- Withdrawn at the EPO - Refused in South Korea
CRIZOTINIB FOR USE IN THE TREATMENT OF CANCER	PFIZER INC	2014/00277	14-Jan-2014	14-Jan-2034	Pending	PCT/ IB12/053765	- Withdrawn at the EPO - Refused in South Korea

TIMELINE OF PATENTS GRANTED ON CRIZOTINIB



14+15. TRASTUZUMAB AND TRASTUZUMAB EMTANSINE

TRASTUZUMAB PRICE AND AVAILABILITY IN SOUTH AFRICA

Trastuzumab is recommended as an essential treatment by the WHO and in South Africa for the treatment of HER2+ breast cancer. Currently only Roche's trastuzumab originator and clone products are available in South Africa, sold under the brand names Herceptin and Herclon respectively.

Herceptin is sold in South Africa's private sector for ZAR 23,562 per 440mg vial, or ZAR 471,240 for a full treatment course. During 2016 Herceptin was the third highest driver of medicine expenditure by private medical aid schemes in South Africa.[63]

Roche's clone product Herclon is sold at ZAR 10,596 – or ZAR 211,920 for a full treatment course. However, this product is only marketed to public sector facilities able to procure the treatment from their facility budget and not offered to private sector users. South Africa's Department of Health is currently negotiating with Roche for a lower price to allow for broad public sector access.

Currently the cost of biosimilar trastuzumab products in India are similar to the cost of Herclon in South Africa – although it can be anticipated that the cost of biosimilar trastuzumab products will decline as their use increases globally as biosimilar products receive pre-qualification by the WHO[64] and registration approval by stringent regulatory authorities.[65]

TRASTUZUMAB PRICES				
Dosage and formulation	Originator product prices in SA private sector	Originator product prices in SA public sector	Generic prices in Canada (if available)	Generic prices in India (if available)
trastuzumab 440mg injection	ZAR 23,562 (Roche)	ZAR 10,596 (Roche)	N/A	Rs 57,500 (Biocon, Mylan) ZAR 11,687

TRASTUZUMAB EMTANSINE PRICE AND AVAILABILITY IN SOUTH AFRICA

Trastuzumab emtansine, also known as T-DM1, is "is an antibody-drug conjugate consisting of the monoclonal antibody trastuzumab linked to the cytotoxic agent emtansine."[66] Trastuzumab emtansine is not yet registered in South Africa. However, in the US where trastuzumab emtansine was registered in 2013, it is indicated for metastatic HER2+ patients that have received prior therapy for metastatic disease, or developed disease recurrence during or within six months of completing adjuvant therapy.[67]

Currently no biosimilar versions of trastuzumab emtansine are available in South Africa, India, the US, Canada, or the EU. However, civil society groups in the United Kingdom are seeking a compulsory license to allow for manufacture and use of biosimilar trastuzumab emtansine.[68]

TRASTUZUMAB EMTANSINE PRICES				
Dosage and formulation	Originator product prices in SA private sector	Originator product prices in SA public sector	Generic prices in Canada (if available)	Generic prices in India (if available)
N/A	N/A	N/A	N/A	N/A

PATENTS GRANTED ON TRASTUZUMAB AND TRASTUZUMAB EMTANSINE IN SOUTH AFRICA

The primary patent on trastuzumab was filed in 1992 in the US and EU.[69] [70] Our research did not identify a matching patent applied for in South Africa. Six secondary patent monopolies held by Roche and Genentech (which provides exclusive marketing rights to Roche) were granted in South Africa between 2000 and 2016. Granted patents could inhibit broad use of biosimilar trastuzumab and trastuzumab emtansine products in South Africa until 2036 – 44 years after the primary patent was granted in the

US and EU and 36 years after the initial patent was granted in South Africa. Secondary patents granted and upheld in South Africa include patents that were withdrawn in India, South Korea and Europe, as well as a patent refused in South Korea.

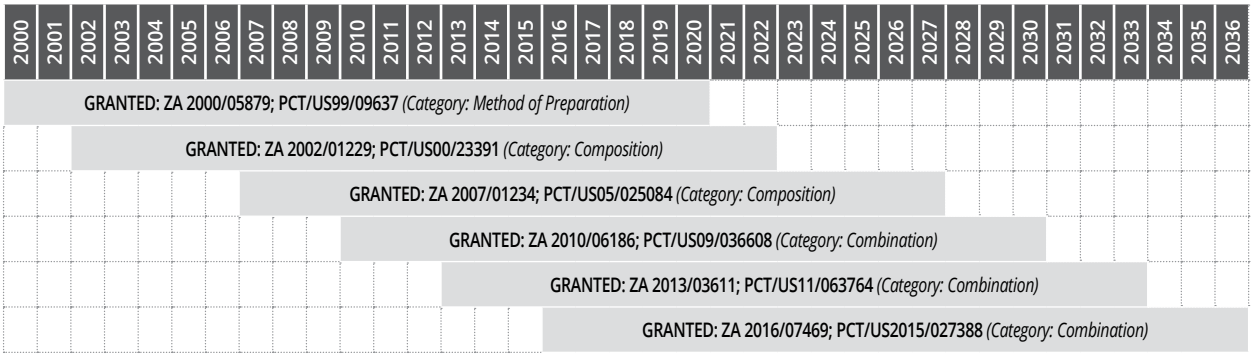
In 2017 Roche granted a global license that will allow for use of Mylan's biosimilar trastuzumab in South Africa following its registration.[71] The license was granted as part of a settlement agreement in which Mylan agreed to withdraw its legal challenges against two trastuzumab products in the US.[72] While the license will allow for introduction of Mylan's biosimilar trastuzumab in South Africa following its registration, it is unlikely that the introduction of this product will lead to significant price reductions if patents remain a barrier to the entry of other competitor products.[73]

PATENTS GRANTED ON TRASTUZUMAB AND TRASTUZUMAB EMTANSINE IN SOUTH AFRICA

Patent Title	Patent Holder	CIPC Number	Lodging Date	Expiry Date	Legal Status	PCT Number	Territories where matching patents withdrawn or refused
PROTEIN PURIFICATION BY ION EXCHANGE CHROMATOGRAPHY	Genentech Inc.*	2000/05879	20-Oct-2000	20-Oct-2020	Granted	PCT/ US99/09637	- Withdrawn in India following CL consideration[74]
DOSAGES FOR TREATMENT WITH ANTI-ERBB2 ANTIBODIES	Genentech Inc.	2002/01229	13-Feb-2002	13-Feb-2022	Granted	PCT/ US00/23391	- Withdrawn in South Korea
HER-2 ANTIBODY COMPOSITION	Genentech Inc.	2007/01234	2-Feb-2007	2-Feb-2027	Granted	PCT/ US05/025084	- Withdrawn in South Korea
COMBINATIONS OF AN ANTI-HER-2 ANTIBODY-DRUG CONJUGATE AND CHEMOTHERAPEUTICAGENTS, AND METHODS OF USE	Genentech Inc.	2010/06186	30-Aug-2010	30-Aug-2030	Granted	PCT/ US09/036608	- Refused in South Korea
TREATMENT OF HER-2-POSITIVE CANCER WITH PACLITAXEL AND TRASTUZUMAB-MCC-DM1	Genentech Inc.	2013/03611	17-May-2013	17-May-2033	Granted	PCT/ US11/063764	- Withdrawn at the EPO - Withdrawn in Korea
METHODS OF TREATING EARLY BREAST CANCER WITH TRASTUZUMAB-MCC-DM1 AND PERTUZUMAB	Genentech Inc.	2016/07469	28-Oct-2016	28-Oct-2036	Granted	PCT/ US2015/027388	- Under examination at EPO

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

TIMELINE OF PATENTS GRANTED ON TRASTUZUMAB AND/OR TRASTUZUMAB EMTANSINE



16. LAPATINIB

LAPATINIB PRICE AND AVAILABILITY

Lapatinib is indicated for the treatment of advanced or metastatic HER2+ breast cancer. In South Africa, only GlaxoSmithKline's originator lapatinib product is available, sold under the brand name Tyverb. Lapatinib is only available in South Africa's private sector.

Lapatinib treatment generally involves taking five 1250 – 1500 mg tablets daily for as long as clinical benefit is provided. At doses of 1500 mg daily, a year of lapatinib treatment would cost around ZAR 351,735. No generic lapatinib products were identified in South Africa, India, the US, EU or Canada. However, health economists from the University of Liverpool have estimated that with broad generic competition, lapatinib can be produced and sold profitably for around ZAR 52,260 per year.[75]

LAPATINIB PRICES

Dosage and formulation	Originator product prices in SA private sector	Originator product prices in SA public sector	Generic prices in Canada (if available)	Generic prices in India (if available)
lapatinib 250mg tablet	ZAR 160.61 (GSK)	N/A	N/A	N/A

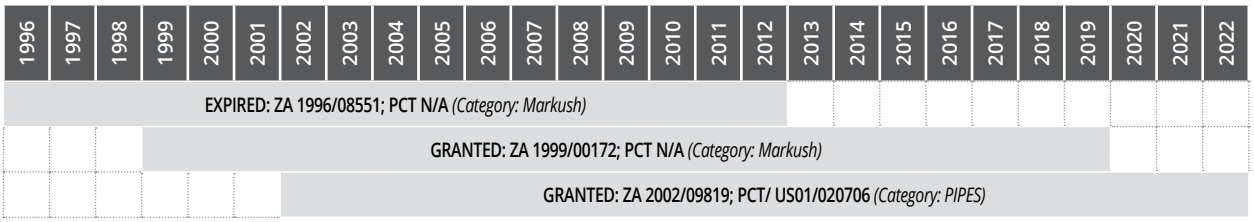
PATENTS GRANTED ON LAPATINIB IN SOUTH AFRICA

Three patents related to lapatinib were granted in South Africa between 1996 and 2002 -including patent PCT/US01/020706 which was rejected in India following patent opposition. With strong patentability criteria, examination and opposition procedures as proposed in the 2017 draft IP Policy, ongoing patents on lapatinib may not have been granted allowing for earlier generic entry.

PATENTS GRANTED ON LAPATINIB IN SOUTH AFRICA

Patent Title	Patent Holder	CIPC Number	Lodging Date	Expiry Date	Legal Status	PCT Number	Territories where matching patents withdrawn or refused
HETEROCYCLIC COMPOUNDS	GLAXO GROUP LTD	1996/08551	10-Oct-1996	10-Oct-2012	Expired	N/A	
HETEROCYCLIC COMPOUNDS	SMITHKLINE BEECHAM CORPORATION	1999/00172	11-Jan-1999	11-Jan-2019	Granted	N/A	
QUINAZOLINE DITOSYLATE SALT COMPOUNDS	SMITHKLINE BEECHAM CORPORATION	2002/09819	03-Dec-2002	03-Dec-2022	Granted	PCT/ US01/020706	- Rejected in India following opposition (IN221171)[76]

TIMELINE OF PATENTS GRANTED ON LAPATINIB



17. ABIRATERONE ACETATE

ABIRATERONE ACETATE PRICE AND AVAILABILITY

Abiraterone acetate is indicated for treatment of advanced or metastatic prostate cancer. In South Africa, only Janssen's originator product is available sold under the brand name Zytiga. The product is not available in the public sector and can only be accessed in the private sector.

Abiraterone acetate treatment typically involves 1000 mg daily doses for as long as clinical benefit is provided. At this dose, a year's treatment of abiraterone acetate in South Africa costs around ZAR 466,075. Comparatively, in India a year of generic abiraterone acetate can be procured at prices between ZAR 44,530 to ZAR 261,430 – depending on the product selected.

ABIRATERONE ACETATE PRICES				
Dosage and formulation	**Originator product prices in SA private sector**	**Originator product prices in SA public sector**	**Generic prices in Canada (if available)**	**Generic prices in India (if available)**
abiraterone acetate 250 mg tablet +	ZAR 319.23 (Janssen)	N/A	N/A	Rs 150 (Sun) ZAR 30.49 Rs 237.50 (Cipla) ZAR 48.27 Rs 880.96 (Glenmark) ZAR 179.06

+ price per tablet

PATENTS GRANTED ON ABIRATERONE ACETATE IN SOUTH AFRICA

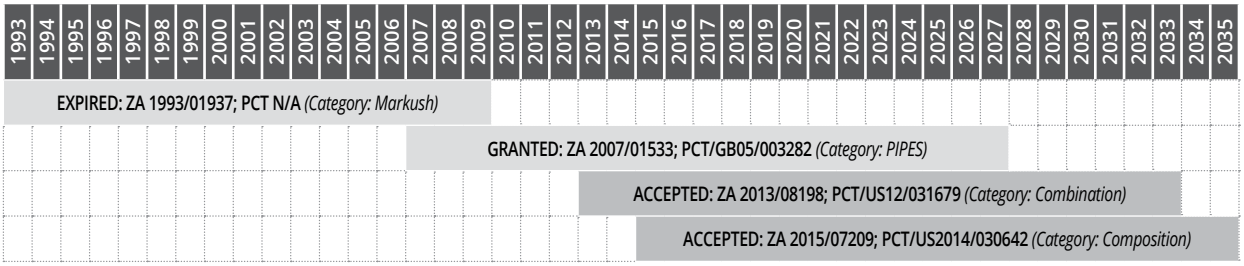
The earliest patent granted on abiraterone acetate was filed by BTG International Ltd (which has licensed Janssen to market abiraterone acetate[77]) in 1993 in South Africa on a Markush claim. Subsequently, BTG International Ltd received an additional secondary patent extending its monopoly protection until 2027 – 34 years after the initial patent was granted. Genentech and Iceutica Inc have also sought secondary patents on abiraterone compositions and combinations for which patent applications have been accepted.

With strong patentability criteria, examination and opposition procedures as proposed in the 2017 draft IP Policy, ongoing patents on abiraterone acetate may not have been granted allowing for earlier generic entry. Additionally, if South Africa reforms its processes for granting compulsory licenses, then compulsory licensing could be used as an expedited mechanism to access more affordable generic abiraterone acetate in the country.

PATENTS GRANTED ON ABIRATERONE ACETATE IN SOUTH AFRICA							
Patent Title	**Patent Holder**	**CIPC Number**	**Lodging Date**	**Expiry Date**	**Legal Status**	**PCT Number**	**Territories where matching patents withdrawn or refused**
17-SUBSTITUTED STREROIDS USEFUL IN CANCER TREATMENT	BTG INTERNATIONAL LIMITED	1993/01937	18-Mar-1993	18-Mar-2009	Expired		
METHANESULFONATE SALTS OF ABIRATERONE-3-ESTERS AND RECOVERY OF SALTS OF ABIRATER ONE-3-ESTERS FROM SOLUTION IN MENTHYL TERT-BUTYL ETHER	BTG INTERNATIONAL LIMITED	2007/01533	21-Feb-2007	21-Feb-2027	Granted	PCT/ GB05/003282	
COMBINATIONS OF AKT INHIBITOR COMPOUNDS AND ABIRATERONE, AND METHODS OF USE	GENENTECH, INC	2013/08198	01-Nov-2013	01-Nov-2033	Accepted	PCT/ US12/031679	
ABIRATERONE ACETATE FORMULATION	ICEUTICA INC.*	2015/07209	29-Sep-2015	29-Sept-2035	Accepted	PCT/ US2014/030642	- Under examination at the EPO

** According to its website, Iceutica Inc's undertakes research on existing treatment to develop "improved efficacy, better side effect profiles and more convenient dosing".*

TIMELINE OF PATENTS GRANTED ON ABIRATERONE ACETATE



18. ENZALUTAMIDE

ENZALUTAMIDE PRICE AND AVAILABILITY

Enzalutamide is indicated for the treatment of metastatic castration resistant prostate cancer. It is not recommended as an essential treatment by the WHO. However, Knowledge Ecology International and the Union for Affordable Cancer Treatment recently motivated for its inclusion.[78] In South Africa only Astellas' enzalutamide product is available, which is sold under the brand name Xtandi. Enzalutamide is not available in the public sector and can only be accessed through the private sector.

Enzalutamide is typically taken in daily doses of 160mg for as long as clinical benefit is provided. At this dose, a year of enzalutamide treatment in South Africa costs ZAR 388,462. No generic products were identified in South Africa, India, the US, or EU – however the Union for Affordable Cancer Treatment is advocating for the National Institute of Health to utilise march-in rights (compulsory licensing) to allow for generic manufacture and use of enzalutamide.[79]

ENZALUTAMIDE PRICES				
Dosage and formulation	**Originator product prices in SA private sector**	**Originator product prices in SA public sector**	**Generic prices in Canada (if available)**	**Generic prices in India (if available)**
enzalutamide 40 mg tablet +	ZAR 266.07 (Astellas)	N/A	N/A	N/A

PATENTS GRANTED ON ENZALUTAMIDE IN SOUTH AFRICA

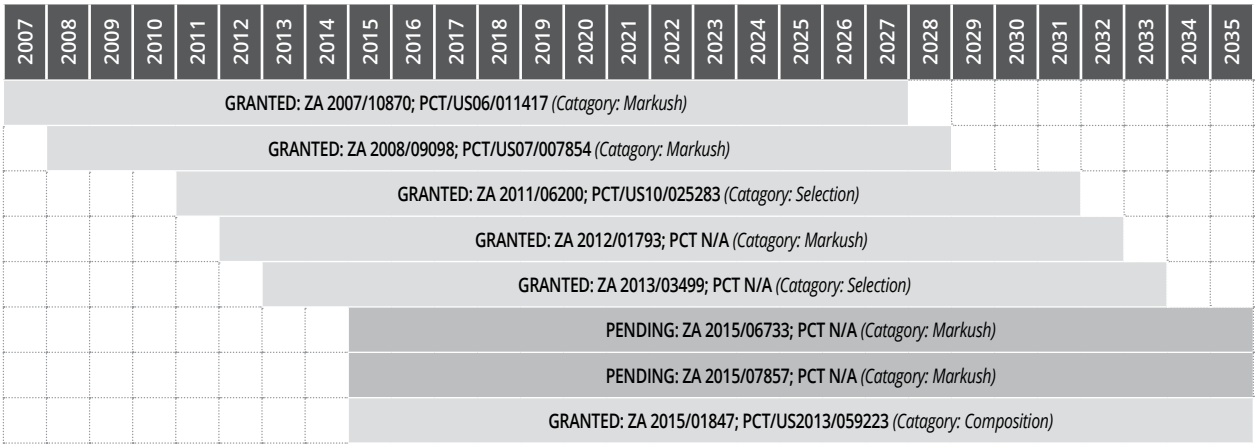
The earliest identified patent granted on enzalutamide in South Africa was granted in 2006. Five additional secondary patents granted on enzalutamide in South Africa to the Regents of the University of California and Medivation Prostate Therapeutics (a licensee of UCLA) extend patent protection on the medicine until 2035 – 29 years after the initial patent was granted.

Patents granted in South Africa include patent PCT/US06/011412 which was opposed and rejected in India and withdrawn in Germany, as well as patent PCT/US10/025283 which was refused in South Korea.

PATENTS GRANTED ON ENZALUTAMIDE IN SOUTH AFRICA							
Patent Title	**Patent Holder**	**CIPC Number**	**Lodging Date**	**Expiry Date**	**Legal Status**	**PCT Number**	**Territories where matching patents withdrawn or refused**
DIARYLHYDANTOIN COMPOUNDS	THE REGENTS OF THE UNIVERSITY OF CALIFORNIA	2007/10870	13-Dec-2007	13-Dec-2027	Granted	PCT/ US06/011417	- Withdrawn in Germany - Rejected in India
DIARYLTHIOHYDANTOIN COMPOUNDS	THE REGENTS OF THE UNIVERSITY OF CALFONIA	2008/09098	23-Oct-2008	23-Oct-2028	Granted	PCT/ US07/007854	
SPECIFIC DIARYLHYDANTOIN AND DIARYL THIOHYDANTOIN COMPOUNDS	MEDIVATION PROSTATE THERAPEUTICS INC *	2011/06200	23-Aug-2011	23-Aug-2031	Granted	PCT/ US10/025283	- Refused in South Korea
DIARYLHYDANTOIN COMPOUNDS	THE REGENTS OF THE UNIVERSITY OF CALIFORNIA	2012/01793	12-Mar-2012	12-Mar-2032	Granted	N/A	
SPECIFIC DIARYLHYDANTOIN AND DIARYLTHIOHYDANTION COMPOUNDS	MEDIVATION PROSTATE THERAPEUTICS INC *	2013/03499	14-May-2013	14-May-2033	Granted	N/A	
DIARYLHYDANTOIN COMPOUNDS	THE REGENTS OF THE UNIVERSITY OF CAIFORNIA	2015/06733	10-Sep-2015	10-Sep-2035	Pending	N/A	
DIARYLHYDANTOIN COMPOUNDS	THE REGENTS OF THE UNIVERSITY OF CAIFORNIA	2015/07857	21-Oct-2015	21-Oct-2035	Pending	N/A	
FORMULATIONS OF ENZALUTAMIDE	BEND RESEARCH, INC.	2015/01847	18-Mar-2015	18-Mar-2035	Granted	PCT/ US2013/059223	- Under examination in EPO

** Medivation Prostate Therapeutics granted a marketing license by UCLA*

TIMELINE OF PATENTS GRANTED ON ENZALUTAMIDE



19. IPILIMUMAB

Ipilimumab is indicated for the treatment of metastatic melanoma. In South Africa, only Bristol-Myers Squibb's ipilimumab product is available, sold under the brand name Yervoy. Yervoy is not available in the public sector and can only be accessed in the private sector.

A 200mg vial of Yervoy is the most expensive medicine in South Africa by unit price.[80] In the private sector, a single 50 mg vial (5mg/ml) and 200 mg vial (5mg/ml) cost ZAR 48,050 and ZAR 192,200 respectively.

No generic ipilimumab products were identified in South Africa, India, the US, Canada, and the EU.

IPILIMUMAB PRICES				
Dosage and formulation	**Originator product prices in SA private sector**	**Originator product prices in SA public sector**	**Generic prices in Canada (if available)**	**Generic prices in India (if available)**
5 mg/ml infusion (10 ml) +	ZAR 4,805 (BMS)	N/A	N/A	N/A
5 mg/ml infusion (10 ml) ++	ZAR 48,050 (BMS)	N/A	N/A	N/A
5 mg/ml infusion (40 ml) +	ZAR 4,805 (BMS)	N/A	N/A	N/A
5 mg/ml infusion (40 ml) ++	ZAR 192,200 (BMS)	N/A	N/A	N/A

+ price per ml ++ price per infusion

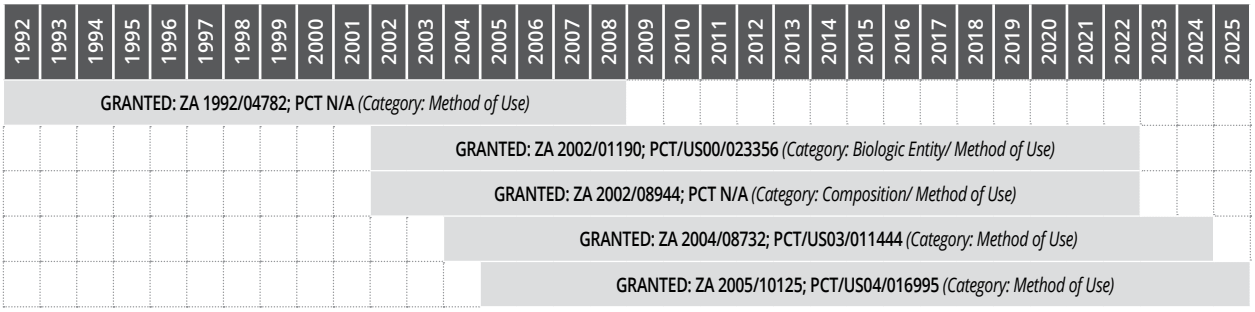
PATENTS GRANTED ON IPILIMUMAB

The development of ipilimumab built on early research related to the use of the CTLA4 receptor, on which patent protection was granted in South Africa in 1992. The primary patent on ipilimumab and its use was granted in 2002. Subsequently, three additional secondary patents related to ipilimumab were granted which could prevent the use of generic ipilimumab in South Africa until 2025 – 33 years after the earliest patent related to ipilimumab was granted in South Africa.

With strong patentability criteria, examination and opposition procedures as proposed in the 2017 draft IP Policy, secondary patents held on ipilimumab in South Africa may not have been granted allowing for earlier generic entry.

PATENTS GRANTED ON IPILIMUMAB IN SOUTH AFRICA							
Patent Title	**Patent Holder**	**CIPC Number**	**Lodging Date**	**Expiry Date**	**Legal Status**	**PCT (or US/EU) number**	**Territories where matching patents withdrawn or refused**
CTLA4 RECEPTOR AND METHODS FOR ITS USE	BRISTON-MYERS SQUIBB COMPANY	1992/04782	26-Jun-1992	26-Jun-2008	Granted	A61K C07K C12N C12P	
HUMAN CTLA-4 ANTIBODIES AND THEIR USE	E. R. SQUIBB & SONS, L.L.C.	2002/01190	12-Feb-2002	12-Feb-2022	Granted	PCT/ US00/023356	- Refused in South Korea
SOLUBLE CTLA4 MUTANT MOLECULES AND USES THEREOF	BRISTOL-MYERS SQUIBB COMPANY	2002/08944	04-Nov-2002	04-Nov-2022	Granted	US20030219863 A1	- Withdrawn in Lithuania
METHODS OF TREAMENT USING CTLA-4 ANTIBODIES	E. R. SQUIBB & SONS, L.L.C.	2004/08732	28-Oct-2004	28-Oct-2024	Granted	PCT/ US03/011444	- Refused in South Korea
SURROGATE THERAPEUTIC ENDPOINT FOR ANTI-CTLA-4 BASED IMMUNOTHERAPY OF DISEASE	E. R. SQUIBB & SONS, L.L.C.	2005/10125	13-Dec-2005	13-Dec-2025	Granted	PCT/ us04/016995	- Under examination at the EPO

TIMELINE OF PATENTS GRANTED ON IPILIMUMAB



20. SORAFENIB

SORAFENIB PRICE AND AVAILABILITY

Sorafenib is indicated for the treatment of advanced renal cell carcinoma and advanced inoperable hepatocellular carcinoma. In South Africa, only Bayer's originator version of sorafenib is available, sold under the brand name Nexavar. Nexavar is not available in the public sector and can only be accessed in the private sector.

Sorafenib is generally provided at 800mg daily for as long as clinical benefit is provided. At this dose, a year of sorafenib treatment in South Africa costs approximately ZAR 334,720. Comparably, in India where generics are already available, a year of sorafenib treatment costs around ZAR 21,900.

SORAFENIB PRICES				
Dosage and formulation	**Originator product prices in SA private sector**	**Originator product prices in SA public sector**	**Generic prices in Canada (if available)**	**Generic prices in India (if available)**
sorafenib 200mg tablet	ZAR 229.26 (Bayer)	N/A	N/A	Rs 57 (Cipla) ZAR 11.59 Rs 74 (Natco) ZAR 15.04

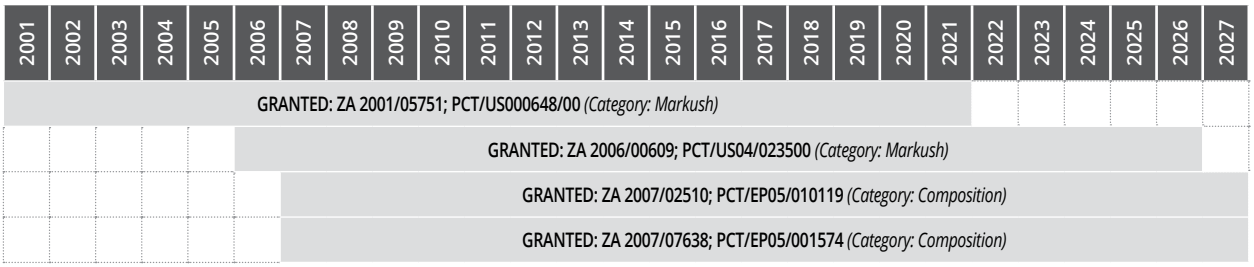
PATENTS GRANTED ON SORAFENIB IN SOUTH AFRICA

Sorafenib was identified as a candidate for cancer treatment in 1999[81] and initially patented in South Africa in 2001. Three additional secondary patents were subsequently granted in South Africa that may prevent the use of generic products in the country until 2027 – 26 years after the earliest identified patent was granted. Patents granted in South Africa, include patent PCT/US000648/00 on which a compulsory license was granted in India, allowing for generic production and use in the country.

With strong patentability criteria, examination and opposition procedures as proposed in the 2017 draft IP Policy, it is likely that some of the secondary patents on sorafenib would not have been granted in South Africa allowing for earlier entry of generic products. Additionally, if South Africa reforms its processes for granting compulsory licenses, then compulsory licensing could be used as an expedited mechanism to access more affordable generic sorafenib in South Africa – as was done in India.

PATENTS GRANTED ON SORAFENIB IN SOUTH AFRICA							
Patent Title	**Patent Holder**	**CIPC Number**	**Lodging Date**	**Expiry Date**	**Legal Status**	**PCT Number**	**Territories where matching patents withdrawn or refused**
CARBOXYARYL SUBSTITUTED DIPHENYL UREAS AS RAF KINASE INHIBITORS	Bayer	2001/05751	12-Jul-2001	12-Jul-2021	Granted	PCT/ US000648/00	- Compulsory license granted in India
FLUORO SUBSTITUTED OMEGA-CARBOXYARYL DISPHENYL UREA FOR THE TREATMENT AND PREVENTION OF DISEASES AND CONDITIONS	Bayer	2006/00609	02-Jan-2006	02-Jan-2026	Granted	PCT/ US04/023500	
THERMODYNAMICALLY STABLE FORM OF BAY 43-90006 TOSYLATE	Bayer	2007/02510	27-Mar-2007	27-March-2027	Granted	PCT/ EP05/010119	- Opposed in India[82]
PHARMACEUTICAL COMPOSITION COMPRISING AN AMEGA-CARBOXYARYL SUBSTITUTED DIPHENYL UREA FOR THE TREATMENT OF CANCER	Bayer	2007/07638	05-Sep-2007	5-Sep-2027	Granted	PCT/ EP06/001574	

TIMELINE OF PATENTS GRANTED ON SORAFENIB IN SOUTH AFRICA



21. BEVACIZUMAB

BEVACIZUMAB PRICE AND AVAILABILITY

Bevacizumab is indicated as a treatment to inhibit the activity of the human vascular endothelial growth factor (VEGF), thereby inhibiting tumour growth. Bevacizumab is recommended as an essential treatment by the WHO for anti-VEGF treatment. In South Africa, bevacizumab is not listed as an essential treatment for a cancer related indication but is recommended as an essential treatment for sub-retinal neovascular membranes and non-resolving macular odema.

In South Africa, only Roche's originator product is available sold under the brand name Avastin, which is available in both the public and private sectors. A single 100mg/4ml infusion costs ZAR 4,440 in South Africa's private sector and ZAR 2,784 in South Africa's public sector. Biosimilars in India are currently more expensive than the originator product in South Africa.

BEVACIZUMAB PRICES

Dosage and formulation	Originator product prices in SA private sector	Originator product prices in SA public sector	Generic prices in Canada (if available)	Generic prices in India (if available)
100mg/4ml infusion ++	ZAR 4,440 (Roche)	ZAR 2,784 (Roche)	N/A	Rs 28,450 (Hetero) ZAR 5,783 Rs 24,752 ZAR 5,030
400mg/16ml infusion ++	ZAR 17,759 (Roche)	N/A	N/A	N/A

++ price per infusion

PATENTS GRANTED ON BEVACIZUMAB IN SOUTH AFRICA

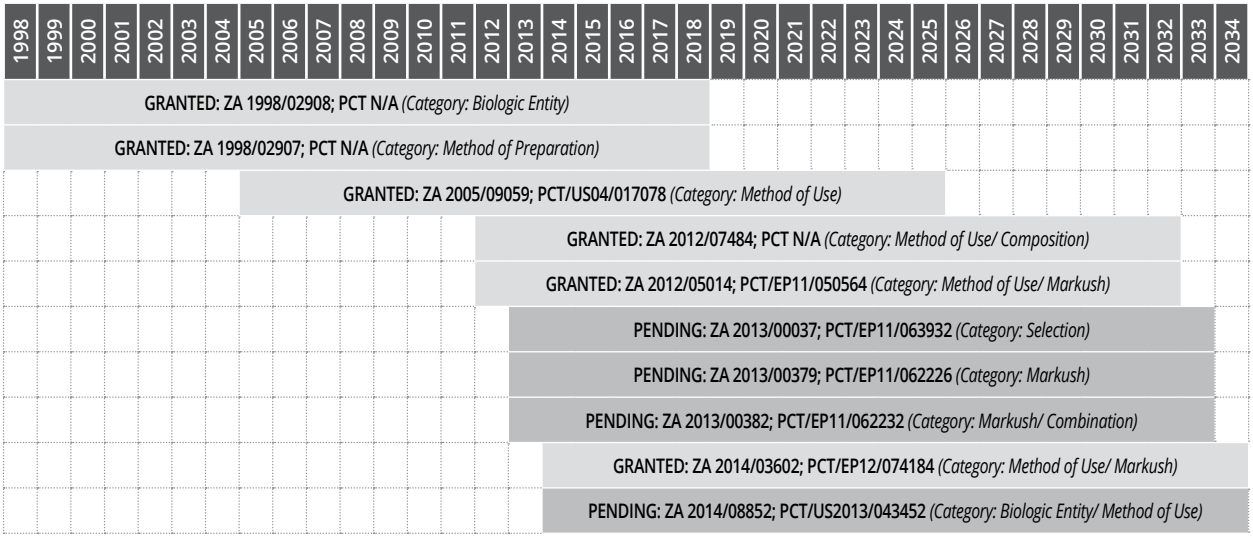
Bevacizumab's primary patent granted on 'Anti VEGF antibodies' was granted in 1998. Five additional granted patents could block the use of biosimilar bevacizumab in South Africa until 2034 – 36 years after the earliest identified patent related to bevacizumab was granted. Patents granted and upheld in South Africa, include patents withdrawn in Europe and South Korea.

With strong patentability criteria, examination and opposition procedures as proposed in the 2017 draft IP Policy, it is likely that some of the secondary patents on bevacizumab would not have been granted in South Africa allowing for earlier entry of generic products.

PATENTS GRANTED ON BEVACIZUMAB IN SOUTH AFRICA							
Patent Title	**Patent Holder**	**CIPC Number**	**Lodging Date**	**Expiry Date**	**Legal Status**	**PCT Number**	**Territories where matching patents withdrawn or refused**
ANTI VEGF ANTIBODIES	GENENTECH INC	1998/02908	06-Apr-1998	06-Apr-2018	Granted	N/A	
HUMANIZED ANTIBODIES AND METHODS FOR FORMING HUMANIZED ANTIBODIES	GENENTECH INC	1998/02907	07-Apr-1998	07-Apr-2018	Granted	N/A	
TREATMENT WITH ANTI-VEGF ANTIBODIES	GENENTECH INC	2005/09059	09-Nov-2005	09-Nov-2025	Granted	PCT/ US04/017078	- Withdrawn at the EPO - Rejected in South Korea
HUMANIZED ANTI-EGFL7 ANTIBODIES AND METHODS USING SAME	GENENTECH INC	2012/07484	05-Oct-2012	05-Oct-2032	Granted	N/A	
TUMOUR TISSUE BASED BIOMARKERS FOR BEVACIZUMAB COMBINATION THERAPIES	F. HOFFMANN-LA ROCHE AG	2012/05014	04-Jul-2012	04-Jul-2032	Granted	PCT/ EP11/050564	- Withdrawn at the EPO
NEUROPILIN AS A BIOMARKER FOR BEVACIZUMAB COMBINATION THERAPIES	F. HOFFMANN LA ROCHE AG	2013/00037	02-Jan-2013	02-Jan-2033	Pending	PCT/ EP11/063932	- Withdrawn at the EPO - Withdrawn in South Korea
BLOOD PLASMA BIOMARKERS FOR BEVACIZUMAB COMBINATION THERAPIES FOR TREATMENT OF PANCREATIC CANCER	F. HOFFMANN LA ROCHE AG	2013/00379	15-Jan-2013	15-Jan-2033	Pending	PCT/ EP11/062226	
BLOOD PLASMA BIOMARKERS FOR BEVACIZUMAB COMBINATION THERAPIES FOR TREATMENT OF BREAST CANCER	F. HOFFMANN LA ROCHE AG	2013/00382	15-Jan-2013	15-Jan-2033	Pending	PCT/ EP11/062232	
BLOOD PLASMA BIOMARKERS FOR BEVACIZUMAB COMBINATION THERAPIES FOR TREATMENT OF BREAST CANCER	F. Hoffmann-La Roche AG	2014/03602	16-May-2014	16-May-2034	Granted	PCT/ EP12/074184	- Withdrawn at the EPO
METHODS OF TREATING CANCER USING PD-L1 AXIS BINDING ANTAGONISTS AND VEGF ANTAGONISTS	GENENTECH, INC	2014/08852	03-Dec-2014	03-Dec-2034	Pending	PCT/ US2013/043452	

Note: Multiple additional patents related to VEGF identified

TIMELINE OF PATENTS GRANTED ON BEVACIZUMAB



22. OCTREOTIDE

Octreotide is indicated for the treatment of acromegaly and gastro-entero-pancreatic neuroendocrine tumours. It is also used to treat flushing and diarrhoea caused by certain types of tumours.[83] In South Africa, octreotide is not listed as an essential treatment for neuroendocrine tumours, but is listed for persistent neonatal hyperinsulinism and hypoglycemia.

Only Novartis's originator octreotide product is available in South Africa, sold under the brand name Sandostatin. While Sandostatin is available in the public and private sectors it can only be accessed in low dose formulations in the public sector.

In South Africa's private sector, a 0.2mg/ml injection and a 30mg injection of octreotide are available at ZAR 3,280 and ZAR 35,594 respectively. Comparably, equivalent biosimilars are available in India and Canada at ZAR 314 and ZAR 4,220 respectively (neither product is available in South Africa's public sector).

OCTREOTIDE PRICES				
Dosage and formulation	**Originator product prices in SA private sector**	**Originator product prices in SA public sector**	**Generic prices in Canada (if available)**	**Generic prices in India (if available)**
octreotide 0.05mg injection	ZAR 218.16 (Novartis)	ZAR 92.94 (Novartis)	CA$ 1.75 (Omega) ZAR 17.36	Rs 195 (United Biotech) ZAR 39.63 Rs 305 (Sun) ZAR 61.99
octreotide 0.1mg injection	ZAR 401.86 (Novartis)	ZAR 177.33 (Novartis)	CA$ 3.30 (Omega) ZAR 32.74	Rs 403.37 (United Biotech) ZAR 81.99 Rs 550 (Sun) ZAR 111.79
octreotide 0.2 mg/ml injection (5ml)	ZAR 3,280 (Novartis)		CA 31.71 (Omega) ZAR 314.56	N/A
octreotide 10mg injection	ZAR 17,255 (Novartis)	N/A	N/A	N/A
octreotide 20mg injection	ZAR 26,539 (Novartis)	N/A	N/A	Rs 20228 (Sun) ZAR 4,111
octreotide 30mg injection	ZAR 35,594 (Novartis)	N/A	N/A	Rs 20762 (Sun) ZAR 4,220

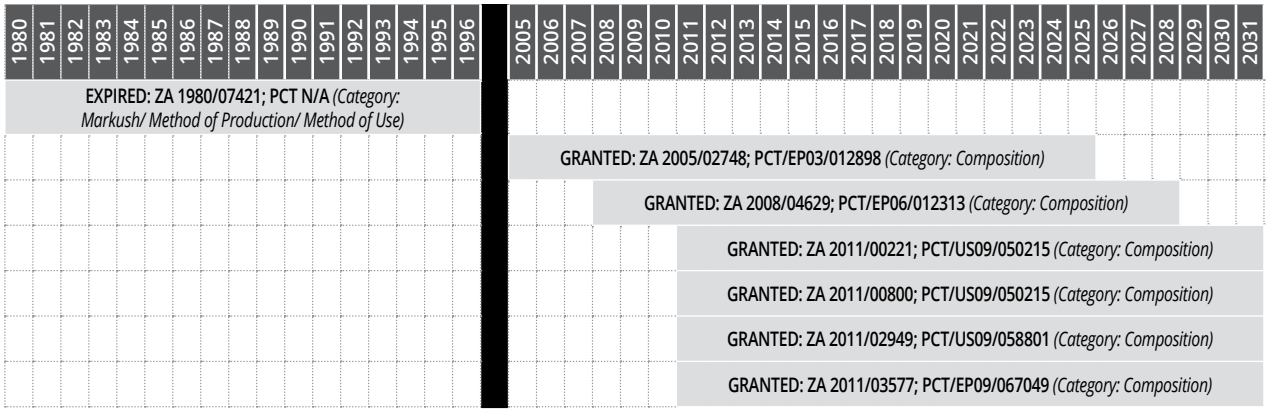
PATENTS GRANTED ON OCTREOTIDE IN SOUTH AFRICA

Octreotide was synthesized in 1979[84] and the initial patent on octreotide was granted in South Africa in 1980. Subsequently six additional secondary patents on octreotide have been granted in South Africa extending patent protection until 2031 – 51 years after the initial patent was granted. Secondary patents granted in South Africa include patents withdrawn in Europe and Germany and rejected in Europe and South Korea.

With strong patentability criteria, examination and opposition procedures as proposed in the 2017 draft IP Policy, it is likely that some of the secondary patents in South Africa would not have been granted allowing for earlier entry of generic products. Additionally, if South Africa reforms its processes for granting compulsory licenses, then compulsory licensing could be used as an expedited mechanism to access more affordable generic octreotide in South Africa.

PATENTS GRANTED ON OCTREOTIDE IN SOUTH AFRICA							
Patent Title	**Patent Holder**	**CIPC Number**	**Lodging Date**	**Expiry Date**	**Legal Status**	**PCT Number**	**Territories where matching patents withdrawn or refused**
Novel polypeptides, processes for their production, pharmaceutical compositions comprising said polypeptides and their use	SANDOZ LTD	1980/07421	27-Nov-1980	27-Nov-2000	Expired	N/A	
PHARMACEUTICAL COMPOSITION COMPRISING OCTREOTIDE MICROPARTICLES	NOVARTIS AG	2005/02748	05-Apr-2005	05-Apr-2025	Granted	PCT/ EP03/012898	- Examination in progress at the EPO
SUSTAINED RELEASE FORMULATION COMPRISING OCTREOTIDE AND TWO OR MORE POLYLACTIDE-CO-GLYCOLIDE POLYMERS	NOVARTIS AG	2008/04629	28-May-2008	28-May-2028	Granted	PCT/ EP06/012313	- Withdrawn in Germany (opposition rejected by the EPO)
OCTREOTIDE IMPLANT HAVING A RELEASE AGENT	ENDO PHARMACEUTICALS	2011/00221	07-Jan-2011	07-Jan-2031	Granted	PCT/ US09/048484	
DELIVERY OF DRY FORMULATIONS OF OCTREOTIDE	ENDO PHARMACEUTICALS	2011/00800	31-Jan-2011	31-Jan-2031	Granted	PCT/ US09/050215	- Withdrawn in the EPO
IMPLANTABLE DEVICE FOR THE DELIVERY OF OCTREOTIDE AND METHODS OF USE THEREOF	ENDO PHARMACEUTICALS	2011/02949	19-Apr-2011	19-Apr-2031	Granted	PCT/ US09/058801	- Refused in South Korea
OCTREOTIDE DEPOT FORMULATION WITH CONSTANTLY HIGH EXPOSURE LEVELS	NOVARTIS AG	2011/03577	16-May-2011	16-May-2031	Granted	PCT/ EP09/067049	

TIMELINE OF PATENTS GRANTED ON OCTREOTIDE



23+24. FILGRASTIM AND PEGFILGRASTIM

FILGRASTIM PRICE AND AVAILABILITY

Filgrastim is recommended as an essential treatment by the WHO for "1. Primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy; 2. Secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy; 3. To facilitate administration of dose dense chemotherapy regimens". In South Africa, filgrastim is recommended as an essential treatment for "1. peripheral blood stem cell harvesting in autologous stem cell harvesting in haematological malignancies and 2. chemotherapy-induced febrile neutropenia."

PEGfilgrastim is the PEGylated form of filgrastim. It is used for the same indications as filgrastim and is more soluble and has prolonged circulatory activity (reduced renal clearance).[85]

Only Amgen's filgrastim and pefilgrastim are available in South Africa sold under the brand names Neupogen and Neulastim respectively. A 300mg injection of filgrastim cost ZAR 1,493 in South Africa's private sector and ZAR 464 in South Africa's public sector. Biosimilar product prices in India are similar to South Africa's public sector price.

A 6mg/0,6ml syringe of pegfilgrastim costs ZAR 8,544 in South Africa. Cheaper biosimilar products in India are available at prices between ZAR 1,728 to ZAR 1,835. This product is not available in South Africa's public sector.

FILGRASTIM PRICES				
Dosage and formulation	**Originator product prices in SA private sector**	**Originator product prices in SA public sector**	**Generic prices in Canada (if available)**	**Generic prices in India (if available)**
filgrastim 300 mcg injection (0,5 ml vial) +	ZAR 2,150 (Amgen)	N/A	N/A	Rs 2288 (Ranbaxy) ZAR 465.04 Rs 2450 (Biocon) ZAR 497.97
filgrastim 300 mcg injection (1 ml vial) +	ZAR 1,493 (Amgen)	ZAR 464.08 (Amgen)	N/A	Rs 2245 (Emcure) ZAR 456.30 Rs 2,249 (Dr Reddy) ZAR 457.11 Rs 2562 (Lupin) ZAR 520.73
filgrastim 480 mcg injection (0,5 ml vial) +	ZAR 3,323 (Amgen)	ZAR 717.38 (Amgen)	N/A	N/A

+ price per vial / prefilled syringe

PEGFILGRASTIM PRICES				
Dosage and formulation	**Originator product prices in SA private sector**	**Originator product prices in SA public sector**	**Generic prices in Canada (if available)**	**Generic prices in India (if available)**
pegfilgrastim 6mg/0,6ml pre-filled syringe ++	ZAR 8,544 (Amgen)	N/A	N/A	Rs 8504 (Lupin) ZAR 1,728 Rs 8809 (Emcure) ZAR 1,790 Rs 9030 (Torrent) ZAR 1,835

+ price per vial ++ price per prefilled syringe

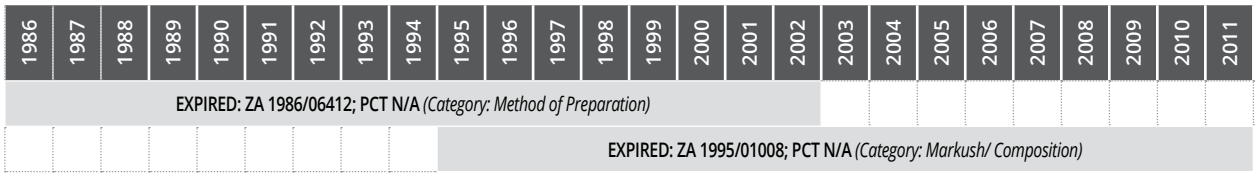
PATENTS GRANTED ON FILGRASTIM AND PEGFILGRASTIM IN SOUTH AFRICA

All identified patents granted on filgrastim and pegfilgrastim have expired. It is unclear why biosimilar products are not available in the country. Further communication should be pursued with biosimilar producers to gain greater insight regarding why biosimilar products are unavailable. Barriers to biosimilar entry may include: 1. ongoing patent barriers that were not identified, 2. regulatory delays and/or 3. lack of interest by biosimilar producers to register and market their products in South Africa.

PATENTS GRANTED ON FILGRASTIM AND PEGFILGRASTIM IN SOUTH AFRICA

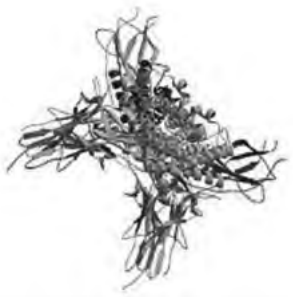
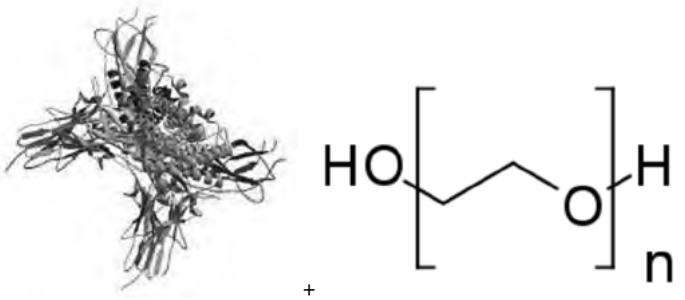
Patent Title	Patent Holder	CIPC Number	Lodging Date	Expiry Date	Legal Status	PCT Number	Territories where matching patents withdrawn or refused
PRODUCTION OF PLURIPOTENT GRANULOCYTE COLONY-STIMULATING FACTOR	KIRIN-AMGEN INCORPORATED	1986/06412	25-Aug-1986	25-Aug-2002	Expired	N/A	
N-TERMINALLY CHEMICALLY MODIFIED PROTEIN COMPOSITION AND METHODS	Amgen Inc	1995/01008	08-Feb-1995	00-Feb-2011	Expired	N/A	

TIMELINE OF PATENTS GRANTED ON FILGRASTIM AND PEGFILGRASTIM



RELATIONSHIP BETWEEN FILGRASTIM AND PEGFILGRASTIM

Filgrastim is a granulocyte colony-stimulating factor (G-CSF) that stimulates the bone marrow to produce more white blood cells (neutrophils). These are necessary as part of the body's immune system. When in low supply, the body is immuno-compromised and is susceptible to infections. This shortage in supply may be as a result of chemotherapy or radiation poisoning, in the case of cancers. PEGfilgrastim is the PEGylated form of filgrastim. It is more soluble and has prolonged circulatory activity (reduced renal clearance).

Filgrastim	Pegfilgrastim
	 +

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Generic imatinib approved by Health Canada was shown to be bioequivalent to originator product Gleevec. See Generic Imatinib Review of the Literature on Clinical Efficacy – Mario de Lemos ML, http://www.capho.org/sites/default/files/nops/Generic%20Imatinib%20Review%20of%20the%20Literature%20on%20Clinical%20Efficacy%20-%20Mario%20de%20Lemos.pdf

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33. *See* e.g., Radhakrishnan P., Pharma's secret weapon to keep drug prices high, STAT News (June 14, 2016), available at https://www.statnews.com/2016/06/14/secondary-patent-gilead-sovaldi-harvoni/; Kapczynski A, Park C & Sampat B. Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of "Secondary" Pharmaceutical Patents. PLoSONE 7(12): e49470. doi:10.1371/journal.pone.0049470.

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www.canceralliance.co.za

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Endnotes

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