



**FACT SHEET**

# LYMPHOMA

**WITH A LOOK AT RITUXIMAB  
AND BENDAMUSTINE ACCESS  
IN SOUTH AFRICA**

**February 2021**



**CANCER  
ALLIANCE**

Collective South African Voices for Cancer

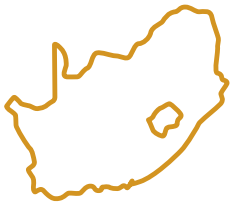
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Lymphoma is a growing problem across the globe and is consistently in the top ten most common cancers. It is however also a curable disease.

In sub-Saharan Africa the increase incidence is associated with the high HIV incidence in the region, the outcomes of lymphoma is however affected by factors such as a possible TB diagnoses coupled with HIV, lack of diagnostic pathways, poor access to treatments at treatment centres that specialise in haematological cancers. Treatment outcomes are in many cases poorer than what it would be in regions that have better access to resources.

The high incidence of HIV in South Africa (7.52 million people) also makes its citizens more vulnerable to lymphoma.

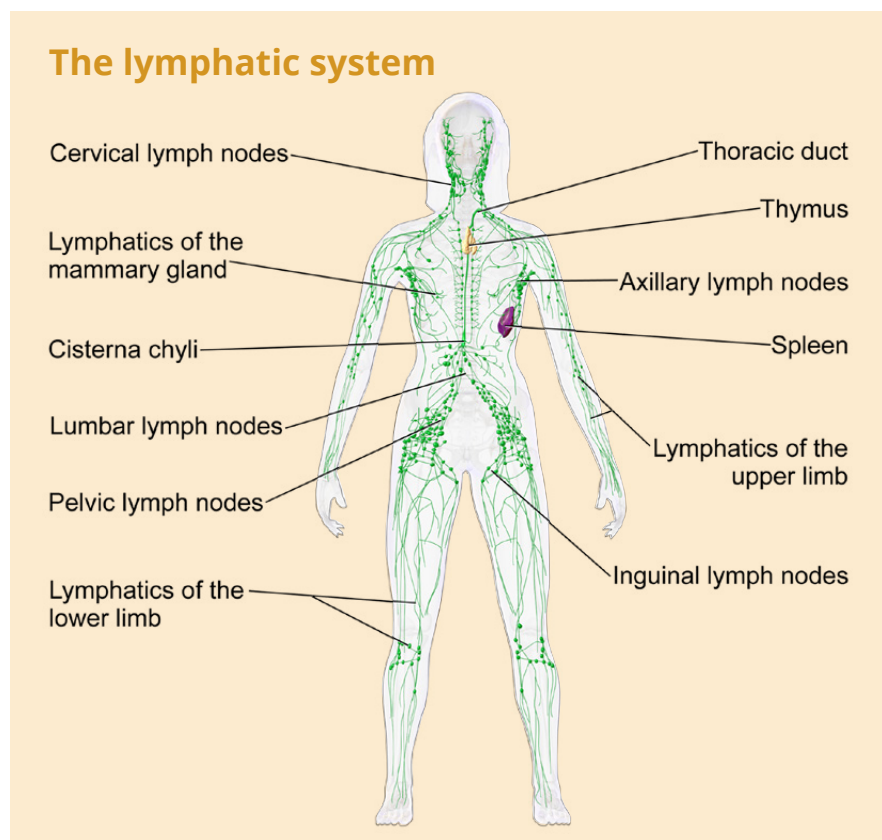
According to the World Health Organisation, South Africa in 2018 reported non-Hodgkin lymphoma represented 3.5% of all cancers and Hodgkin lymphoma 0.42% of all cancers. The National Cancer Registry data is however underreported.

Delayed diagnosis due to gaps in knowledge and inefficient diagnostic methods contribute to preventable suffering and even deaths in patients presenting with lymphoma. The good news is that lymphoma is a very treatable cancer and in the majority of aggressive lymphomas can be cured.

# WHAT IS LYMPHOMA?

Lymphoma is a cancer that arises from the lymphatic system in the body. The lymphatic system consist of about 600 lymph nodes (or glands) and a vast network of vessels that – very much like the vascular system – circulates a fluid throughout the whole body. This fluid is rich in infection-fighting white blood cells, which are the army of the immune system.

Lymphoma is cancer of a lymph node. There are two main types of lymphoma: non-Hodgkin lymphoma and Hodgkin lymphoma. Enlarged lymph nodes (lymph node swelling, also called ‘lymphadenopathy’) is the most common symptom in patients with lymphoma – and could be an indication that cancer cells are present. But lymph node swelling also happens for other reasons, most commonly infection at the site that the lymph node drains.





# SYMPTOMS

These are the most common symptoms that might indicate lymphoma:

- Swollen lymph glands/nodes in the neck, armpits, around the elbow or in the groin.
- Extreme and unexplained weight loss.
- Fever.
- Night sweats.
- Persistent fatigue.
- Shortness of breath.

The presentation of lymphoma symptoms may be non-specific (meaning that these symptoms overlap with many other diseases) or be related directly or indirectly to lymph nodes or other lymphoid tissues.

### NON-SPECIFIC FEATURES

1. Unexplained or unintentional **weight loss**, which is significant if it accounts for more than 10% of body weight in the preceding six months,
2. Unexplained **fever** (a temperature above 38°C) in the preceding two to four weeks.
3. Unexplained, drenching **night sweats** in the past 2 to 4 weeks.
4. Pruritus or **itching** of the body. Lymphoma is one of the many conditions that can present with severe pruritus. Pruritus is a feature that is more commonly seen in Hodgkin lymphoma and T-cell NHL.

### NODAL DISEASE (IN THE LYMPH NODES)

Swollen lymph nodes (lymphadenopathy) – which can happen in just one area of the body or in more than one – is the clinical hallmark of the disease. These swollen lymph nodes are typically painless, mobile, have a firm to rubbery consistency, and are usually larger than 1cm in diameter.

The lymphadenopathy may present as a mass or lump and be evident in areas such as the neck, the armpits, the elbow and the groin. It may also be evident in areas such as the back of the throat, the chest cavity, abdominal area, gonads (testes or ovaries). Sometimes the symptoms caused by the lymph node are from a compression of normal structures around the lymph node.

## **EXTRANODAL DISEASE (OUTSIDE THE LYMPH NODES)**

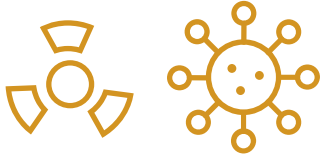
Hodgkin lymphoma usually presents with disease inside the lymph nodes – with more than 70% of individuals having lymphoma in the neck area.

In contrast, 30-40% of patients with the more common non-Hodgkin type of lymphoma initially present with extranodal disease – which means the disease is somewhere other than the lymph nodes. These areas include the gastrointestinal tract, the skin and the central nervous system. However, any extranodal site can potentially be involved by lymphoma including the pleural, pericardial and peritoneal cavities, gonadal tissue, breasts and bones. Extranodal disease occurs in 70-80% of HIV positive people with non-Hodgkin lymphoma.

## **PARANEOPLASTIC OR NON-METASTATIC MANIFESTATIONS**

Lymphoma can also present with unusual manifestations (in the skin or central nervous system for example) but without radiological or histological evidence of lymphoma in the involved site.

This is known as paraneoplastic or non-metastatic disease, as the disease involvement is related to the lymphoma by virtue of the fact that it may improve and respond to the lymphoma treatment, despite there being no anatomical evidence of lymphoma in the involved site.



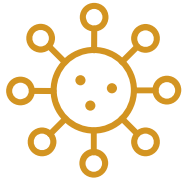
# CAUSES & RISK FACTORS

There is no one underlying cause for lymphoma, but there are clear risk factors:

1. **Immunosuppression or Immunodeficiency**, the most common cause of immune deficiency in our setting is HIV, and the risk of lymphoma is at least 10-fold higher in people living with HIV. Immune deficiency can be from other rarer conditions, such as immunosuppressive drugs for the treatment of cancer, autoimmune diseases or in organ transplant patients and very rarely from congenital causes.
2. In some cases an **abnormal immune system response** to viral infections such as Epstein Barr virus (EBV) are thought to play a role in developing lymphoma, but most people exposed to EBV never develop lymphoma.
3. **Chemicals and radiation** – even though there has been no causative link to the development of lymphoma from commonly used herbicides or pesticides, there may be an association with high dose radiation and certain medications that affect the body's DNA repair mechanisms.

These risk factors vary in different populations and may be inherited (congenital) or acquired.



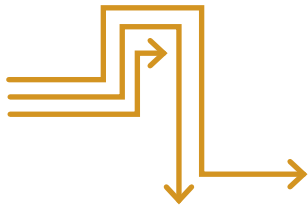


# LYMPHOMA AND HIV

The human immunodeficiency virus (HIV) causes immunodeficiency – which in turn increases the risk of infections and cancer, including lymphoma. HIV may have more direct mechanisms that also contribute to the risk of lymphoma but these have yet to be proven. In South Africa, more than 60% of public sector patients with lymphoma are HIV positive.

High-grade (fast-growing), B-cell non-Hodgkin lymphoma is one of several AIDS-defining illnesses – meaning that it is an indicator that a person living with HIV has developed what is known as advanced HIV disease, or AIDS. In the era of highly active antiretroviral therapy there has been a decrease in the risk of lymphoma, but **lymphoma is still roughly 10 times more likely to develop in someone living with HIV.**

The risk is increased for both Hodgkin and non-Hodgkin lymphoma. Patients with HIV and lymphoma are also at a high risk of being misdiagnosed with TB – in other words the patient may first be told incorrectly that they have TB and only later the diagnosis of lymphoma is made. This happens because many of the symptoms of TB are similar to that of lymphoma (including swollen lymph nodes), and TB is also far more common than lymphoma in people living with HIV.

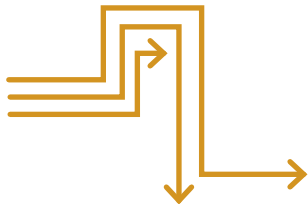


# COMPLICATIONS

Apart from the complications directly related to lymphoma, some may also result from comorbidities such as HIV and tuberculosis or the treatment of these. Here are some of the overall complications people with lymphoma experience:

## SHORT TERM COMPLICATIONS

- **Gastrointestinal** – inflammation and/or ulceration of the mucous membranes along the digestive track, nausea, vomiting, indigestion, gastritis, ulcers, weight gain, weight loss, nutritional abnormalities.
- **Bone marrow suppression** – anaemia, bleeding, infection. An increased risk of infection may also be related to drugs like corticosteroids, or depletion of B-cells and/or reactivation of latent viruses such as hepatitis virus with Rituximab.
- **Alopecia** (hair loss)
- **Peripheral neuropathy** – manifesting as ‘pins and needles’ sensation, tingling or numbness in the fingertips or toes.
- **Gonadal toxicity** – decreased sperm production menstrual abnormalities.
- **Mood and psychosocial changes** – emotional instability, depression, psychosis.
- **Tumour lysis syndrome** and its consequences of electrolyte abnormalities and renal impairment.
- **Other complications** like hearing loss, visual abnormalities, arrhythmias (heart rhythm abnormalities).



## LONG TERM COMPLICATIONS

- **Cardiovascular** – cardiomyopathy (heart muscle dysfunction and heart failure), pericardial disease, ischaemic heart disease
- **Malignancy** – increased risk of myelodysplasia (abnormalities in the blood counts and bone marrow, with an increased risk of developing leukaemia) and second malignancies, such as acute leukaemia and carcinoma (thyroid, lung, breast etc.), consequent to chemotherapy and/or radiotherapy
- **Hypothyroidism** (under-function of the thyroid gland from prior radiotherapy)
- **Respiratory** – lung fibrosis
- **Infertility** and sterility
- **Psychosocial**
- **Growth retardation** and osteopenia/osteoporosis
- **Neurological** – including nerve damage.



## DIAGNOSIS

Lymphoma is usually suspected in anyone with significant swelling in the lymph nodes (lymphadenopathy) and/or has a combination of other symptoms associated with it. If someone is HIV positive, the chances that they may have lymphoma also increases.

However, the definitive diagnosis of lymphoma is made histologically – by looking at tissue cells under a microscope. This tissue biopsy test is absolutely essential to definitively diagnose lymphoma as a number of infective conditions such as tuberculosis and other cancers can mimic the symptoms of lymphoma.

The tissue – usually a biopsy of the lymph node removed surgically or a core biopsied with a thick needle – will also show whether the lymphoma is Hodgkin lymphoma or non-Hodgkin lymphoma. A further and more detailed analysis of the tissue will determine the exact subtype of lymphoma.

**Because TB is so common in South Africa – and therefore prominent in the minds of doctors – many patients are misdiagnosed with TB.**



# STAGING AND GRADING

After establishing a definitive diagnosis of the type and subtype of lymphoma, further investigations are undertaken to define the stage of the disease.

These investigations include blood tests, a bone marrow biopsy and imaging or radiological investigations such as a chest X-ray and CT scan or PET CT scan.

This information is then used to “stage” the patient before deciding on a treatment plan. Additional factors that are also looked at include the age of the patient, performance status, vital organ function and comorbidities.



# TREATMENT OPTIONS

Lymphoma is best managed by a multidisciplinary healthcare team. There are two aspects of treatment: supportive care and specific modalities of treatment.

## SUPPORTIVE CARE

- Psychosocial support
- Educational support
- Pain medication
- Allopurinol to treat and prevent hyperuricaemia (high levels of uric acid in the blood)
- Transfusion of blood and blood products, where indicated
- Treatment of comorbidities such as HIV with combination antiretroviral therapy
- Correction of electrolyte imbalance, where present
- Prevention and treatment of infections.

## SPECIFIC MODALITIES OF TREATMENT

- Chemotherapy
- Monoclonal antibodies (immunotherapy)/targeted therapy
- Radiotherapy
- Surgery
- Stem cell transplantation
- Novel and experimental therapies

## Here is more information on some of the specific modalities of treatment.

### COMBINATION CHEMOTHERAPY

Combination chemotherapy is the basis of treatment for lymphoma. Various combinations have been used in Hodgkin lymphoma and non-Hodgkin lymphoma. The combination of Adriamycin, Bleomycin, Vincristine and Dacarbazine is used to treat Hodgkin lymphoma, while Cyclophosphamide, Hydroxydaunorubicin/ Adriamycin, Oncovin/Vincristine, Prednisone is a typical chemotherapy backbone in non-Hodgkin lymphoma.

Rituximab, used with the aforementioned combination, is now the standard of care in many types of non-Hodgkin lymphoma.

In general, patients with early stage lymphoma (stage I and II disease) receive four to six cycles of initial chemotherapy, while those with advanced stage disease (stage III and IV) are given six to eight cycles.

After treatment patients are monitored and unless there is a complete response, further therapy will be required.

### RADIOTHERAPY

In early stage non-Hodgkin lymphoma, radiotherapy may be used as a single, initial treatment, while in the aggressive lymphomas and Hodgkin lymphoma, radiotherapy is usually given after chemotherapy, to reduce the need for more chemo or to prevent relapse in patients. Radiotherapy can also be used in emergency situations such as spinal cord compression.

### SURGERY

Surgery may be necessary for some patients with spinal cord compression. Surgery may also assist in the diagnosis and treatment of lymphoma causing intestinal obstruction and where lymphoma develops in inaccessible sites like the spleen and a splenectomy may help with a definitive diagnosis.



# ACCESS CHALLENGES IN SOUTH AFRICA

South Africa is a middle-income country plagued by massive economic inequality and corruption. Half of the population lives in poverty – and around 85% rely on a frail and collapsing public healthcare system.

With an estimated 13% of the population living with HIV, less common diseases such as lymphoma are far down the line in an already over-burdened public healthcare system.

Overstretched oncology and haematology services in the smaller provinces need to be expanded, better staffed and better managed. More money is needed for these specialised centres. Diagnostic methods and tools need to be improved – specifically with regards to lymphoma.

Medicine shortages – further exacerbated by overuse, mismanagement, budgetary constraints and exorbitant pricing by big pharma – is a daily reality. Many public sector hospitals in populous and developed provinces such as Gauteng have a large referral base, often from less developed provinces where specialised services like haematology and oncology are lacking. This large patient load is compounded by patients from other countries.

The lymphoma medicine bendamustine is not currently available to public sector patients – despite being listed on the WHO essential medicine list. This is because of weak patent laws in South Africa which allows profit-hungry pharmaceutical companies to gain multiple overlapping patents that extend the length of monopoly and lead to prices government cannot afford. Cancer medicines with specialised indications should also be added to South Africa's essential medicines list which would make new medicines and treatments affordable.





# RITUXIMAB

In South Africa, rituximab is recommended as an essential treatment for CD20 positive B-cell non-Hodgkin's lymphoma, refractory rheumatoid arthritis, and refractory lupus nephritis. The World Health Organisation also recommends rituximab as an essential treatment for chronic lymphocytic leukemia and follicular lymphoma.

Currently only Roche's rituximab products are available in South Africa. Roche markets rituximab products for both intravenous and subcutaneous delivery:



- Intravenous delivery means that a medicine is delivered by IV. An IV administers medicines directly into one's blood stream through a needle inserted into one's vein.



- Subcutaneous delivery means that a medicine is delivered by injection.

Subcutaneous administration is generally preferred by both patients and healthcare workers. It also involves fewer healthcare resources and can be delivered more decentrally than intravenous products.

Roche markets both intravenous and subcutaneous rituximab in South Africa. Only the intravenous product is available in the public sector.

Adcock Ingram recently received authorisation from the South African Health Products Regulatory Authority (SAHPRA) to begin marketing its biosimilar rituximab product in South Africa.<sup>1</sup> While SAHPRA's authorisation of biosimilar rituximab in South Africa is a welcome development that may lead to price reductions for intravenous rituximab products, ongoing patents impede the entry of biosimilar versions of subcutaneous rituximab.



**World Health Organization**

The World Health Organisation has prequalified Celltrion's intravenous rituximab biosimilar products as meeting its standards of safety, efficacy, and quality.

1. Communication with Adcock Ingram



## RITUXIMAB PATENTS

The earliest patent related to rituximab in South Africa was granted in 1984. Subsequently, multiple secondary patents related to rituximab have been granted in the country, including on new uses and new formulations of rituximab, as well as combinations of rituximab with other agents.

In 2012, Roche filed a patent on its reformulated subcutaneous rituximab in South Africa. This patent may extend Roche's market monopoly and block availability of biosimilar subcutaneous products until 2030.

It is not uncommon for pharmaceutical companies to reformulate old medicines and seek secondary patents on the new formulations when their patent monopolies are coming to an end. These secondary patents often lead to inequitable access to, and large price variations between, different versions of the same medicine. As a result, low income populations are often unable to access more tolerable and preferable products.

South Africa can prevent companies from carving up the market for different versions of the same medicines and impeding equitable health care access by amending its patent laws to ensure that only genuine innovations are granted patent monopolies and excluding changes to, or new uses of, existing medicines from patentability.

**South Africa should urgently amend its law to exclude new formulations and uses of existing medicines from patentability as done in other territories.**

Patent title	Patent Holder	CIPC Number	International filing date	Date of application	Expiry Date	Legal Status	PCT Number	Actions in other jurisdictions
Recombinant immunoglobulin preparations	Genentech Inc, City Of Hope	1984/02583	N/A	5-Apr-1984	4-Apr-2004	Expired	N/A	N/A
Chimeric antibody with specificity to human b cell surface antigen	Xoma Corporation	1988/00091	N/A	07-Jan-1988	07-Jan-2008	Expired	N/A	N/A
Therapeutic application of chimeric and radiolabeled antibodies to human b lymphocyte restricted differentiation antigen for treatment of b cell lymphoma	Idec Pharmaceuticals Corporation	1993/08466	N/A	12-Nov-1993	12-Nov-2013	Expired	N/A	N/A
Combination therapies for b cell lymphomas comprising administration of anti cd20 antibody	Idec Pharmaceuticals Corporation	2001/01157	11-Aug-1999	9-Feb-2001	11-Aug-2019	Expired	PCT/US99/18120	Withdrawn in Korea, Withdrawn in Europe
Treatment of hematologic malignancies associated with circulating tumor cells using chimeric anti cd20 antibody	Idec Pharmaceuticals Corporation	2001/03720	9-Nov-1999	8-May-2001	9-Nov-2019	Granted (Renewal payments up to date)	PCT/US99/26308	Refused and withdrawn in Korea, Withdrawn in Europe
Chimeric anti cd20 antibody treatment of patients receiving bmt or pbsc transplants	Idec Pharmaceuticals Corporation	2001/03716	9-Nov-1999	8-May-2001	9-Nov-2019	Granted (Renewal payments up to date)	PCT/US99/24012	Refused in Korea
Use of cd23 antagonists for the treatment of neoplastic disorders	Biogen Idec Inc	2003/05891	31-Jan-2002	30-Jul-2003	31-Jan-2022	Granted (no details regarding renewal payments)	PCT/US02/02620	Withdrawn in Europe, Withdrawn and refused in Korea
Method for treating joint damage	Hoffman La Roche Ag, Genentech Inc, Biogen Idec Inc	2008/04288	14-Nov-2006	19-May-2008	14-Nov-2026	Granted (Renewal payments up to date)	PCT/US06/044290	Refused and withdrawn in Korea, Withdrawn in Europe
Antibody purification by cation exchange chromatography	Genentech Inc	2010/02850	29-Oct-2008	22-Apr-2010	29-Oct-2028	Granted (Renewal payments up to date)	PCT/US08/081516	
Combination therapy with type i and type ii anti-cd20 antibodies	Roche Glycart Ag	2010/01442	20-Aug-2008	26-Feb-2010	20-Aug-2028	Granted (no details regarding renewal payments)	PCT/EP08/006833	Withdrawn in the Philippines
Combination therapy of a type ii anti-cd20 antibody with an anti-bcl-2 active agent	Roche Glycart Ag	2010/02573	13-Oct-2008	13-Apr-2010	13-Oct-2028	Pending	PCT/EP08/008635	Withdrawn in Europe
Combination therapy of a type ii anti-cd20 antibody with a proteasome inhibitor	Roche Glycart Ag	2010/02575	22-Oct-2008	13-Apr-2010	22-Oct-2028	Granted (no details regarding renewal payments)	PCT/EP08/008919	Withdrawn in the Philippines
Highly concentrated pharmaceutical formulations comprising anti-cd20 antibody	Hoffmann-La Roche Ag	2012/01605	10-Sep-2010	02-Mar-2012	10-Sep-2030	Granted (Renewal payments up to date)	PCT/EP10/063271	Refused in Korea

Patent data provided in this table was compiled in October 2019



# BENDAMUSTINE

Bendamustine is recommended as an essential treatment for chronic lymphocytic leukaemia and follicular lymphoma by the World Health Organization.<sup>2</sup> In South Africa, bendamustine is indicated for the treatment of chronic lymphocytic leukaemia, non-Hodgkin's lymphoma, and multiple myeloma<sup>3</sup> – but is not included on South Africa's essential medicines list.<sup>4</sup>

Bendamustine is not available in South Africa's public sector where the vast majority of people in the country access care, most likely due to the high cost of patented products, and can only be accessed in the private sector.

A typical full-course of bendamustine for chronic lymphocytic leukaemia involves intravenous dosing of 100mg for two days in a row, in a 28-day cycle for 6 cycles. In South Africa, where only Astellas's originator products are available, sold under the brand name Ribomustin, a full course of bendamustine costs approximately ZAR 50,616. By comparison a full course of generic bendamustine in India costs approximately ZAR 9,024. Access to generic bendamustine in South Africa could therefore reduce domestic prices by over 80% and substantially improve access.

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2. World Health Organization Model List of Essential Medicines, 2019

3. South African Medicines Formulary 12th Edition

4. Tertiary and Quaternary Level Essential Medicines List, July 2019

## BENDAMUSTINE PRICES

Dosage and formulation	Originator product prices in SA private sector <sup>5</sup>	Originator product prices in SA public sector <sup>6</sup>	Maximum retail price of generics in India <sup>7</sup>
Bendamustine 25mg powder for injection +	R1,055 (Astellas)	N/A	N/A
Bendamustine 100mg powder for injection +	R4,218 (Astellas)	N/A	R752 (Rs 3643, Natco) R1,425 (Rs 6900, Cipla) R1,450 (Rs 7020, Biocon)

+ price per vial

## PATENTS GRANTED ON BENDAMUSTINE IN SOUTH AFRICA

Bendamustine was synthesized in 1963 in East Germany. Following a series of licensing deals and company acquisitions, Astellas and Cephalon (subsequently acquired by Teva) acquired the rights to develop and market bendamustine in 2005.<sup>8</sup>

Six secondary patents related to bendamustine have been granted in South Africa to Astellas and Cephalon on new forms, compositions and medical uses of bendamustine. **If unchallenged, secondary patents granted in South Africa could block access to generic bendamustine access in the country until 2031.**

Patents granted and upheld in South Africa include patents that were withdrawn and refused in other jurisdictions, including in Europe, Israel and Colombia.<sup>9</sup> South Africa commonly grants poor quality patents that are rejected or withdrawn, or granted on a smaller scope of protection, in other jurisdictions given shortcomings in the country's laws and procedures for granting patents.

5. Medicines Price Registry, Database of Medicine Prices 14 October 2019

6. NDoH Master Procurement Catalogue, 4 October 2019

7. [1mg.com](http://1mg.com), 27 October 2019, ZAR 1 = Rs 4,84

8. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2795094/>

9. Wipo Patentscope National Phase data, 24 October 2019



For example, South Africa does not examine the merits of patent applications prior to their granting and as a result commonly grants patents that fail to meet the country's patentability criteria.<sup>10</sup>

Importantly, South Africa adopted a new national IP policy in 2018 that committed to reforming the country's patent laws and procedures to promote public health and health care access in line with the country's Constitutional obligations. Under reforms committed to in the policy, it is likely that many of the secondary patents on bendamustine would not have been granted, allowing for earlier entry of generic products. The 2018 IP policy further commits to the adoption of more efficient and effective procedures for compulsory licensing that could be used to expedite access to generic bendamustine in the country.

**To improve medicine access and affordability, and achieve significant cost savings, South Africa must urgently reform its patent laws in line with its policy commitments.**

Adcock Ingram recently received authorisation from the South African Health Products Regulatory Authority (SAHPRA) to begin marketing a generic product in South Africa.<sup>11</sup> SAHPRA's authorisation of generic bendamustine in South Africa is a welcome development that may lead to price reductions for generic products. Affordability will influence the inclusion on the EML .

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10. Pouris A, Pouris A. (2011). Patents and economic development in South Africa: Managing intellectual property rights. [doi.org/10.4102/sajs.v107i11/12.355](https://doi.org/10.4102/sajs.v107i11/12.355)

11. Communication with Adcock Ingram

Patent title	Patent Holder	CIPC number <sup>12</sup>	PCT number	International filing date	Date of application	Expiry date	Status	Actions in other jurisdictions
Bendamustine pharmaceutical compositions for lyophilisation	Cephalon Inc	2007/05793	PCT/ US06/001308	13/01/2006	13/07/2007	13/01/2026	Accepted (Renewal payments up to date)	Withdrawn in Europe, Withdrawn in Israel, Withdrawn in Korea
Solid dosage forms of bendamustine	Astellas Deutschland GmbH	2011/03790	PCT/ EP09/008639	03/12/2009	24/05/2011	03/12/2029	Granted (Renewal payments up to date)	Refused in Colombia
Oral dosage forms of bendamustine	Astellas Deutschland GmbH	2011/03791	PCT/ EP09/008857	03/12/2009	24/05/2011	03/12/2029	Granted (Renewal payments up to date)	Refused in Colombia
Novel forms of bendamustine free base	Cephalon Inc	2011/05099	PCT/ US10/020992	14/01/2010	11/07/2011	14/01/2030	Granted (Renewal payments up to 14/01/2017)	Withdrawn in Europe, Refused in Korea
Oral dosage forms of bendamustine and therapeutic use thereof	Astellas Deutschland GmbH	2012/08822	PCT/ EP11/002763	01/06/2011	22/11/2012	01/06/2031	Granted (Renewal payments up to date)	Refused in Colombia
Oral dosage forms of bendamustine	Astellas Deutschland GmbH	2012/08823	PCT/ EP11/002764	01/06/2011	22/11/2012	01/06/2031	Granted (Renewal payments up to date)	Refused in Colombia

12. SA patent data sourced from CIPC 24 October 2019

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