A2M

FACTSHEET

MULTIPLE MYELOMA

WITH A LOOK AT LENALIDOMIDE ACCESS IN SOUTH AFRICA

January 2019

CANCER ALLIANCE

Collective South African Voices for Cancer

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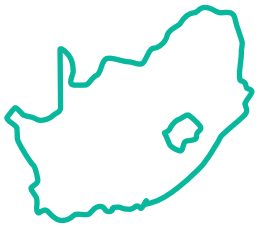
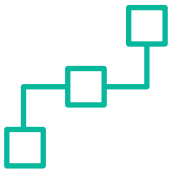


MULTIPLE MYELOMA IN SOUTH AFRICA

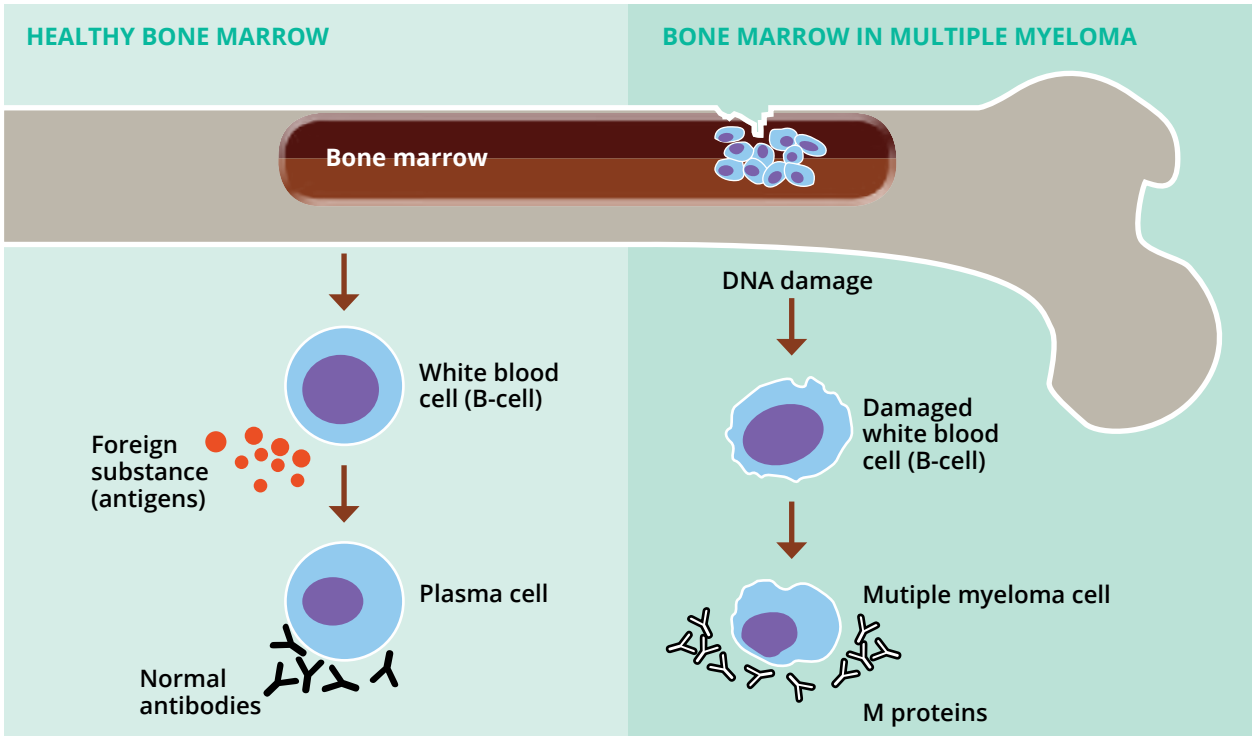
In 2014, there were 347 cases of multiple myeloma diagnosed in the South African population. The lifetime risk for multiple myeloma was 1:969 for men and 1:1090 for women. This is likely an under-estimate of the true incidence as only cases diagnosed with a bone marrow test are reported to the National Cancer Registry.



AETIOLOGY

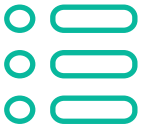
Multiple myeloma is a haematological (blood) cancer that forms in a type of white blood cell in the bone marrow called a plasma cell. Plasma cells help you fight infections by making antibodies that recognise and attack germs.

Multiple myeloma causes cancerous plasma cells to accumulate in the bone marrow, where they crowd out healthy blood cells. Rather than produce helpful antibodies, the cancer cells produce abnormal proteins (M proteins) that can cause complications. These M proteins offer no benefit to the body, and as the amount of M protein increases, it crowds out the production of normally functioning immunoglobulins (antibodies).



In healthy bone marrow, B-cells, a type of white blood cell, develop into antibody-producing plasma cells when foreign substances (antigens) enter the body. In multiple myeloma, DNA damage to a B-cell transforms the normal plasma cell into a multiple myeloma cell. The cancerous cell multiplies, leaving less space for normal blood cells in the bone marrow, and produces large quantities of M protein.

Multiple myeloma typically occurs in bone marrow with the most activity, which is the marrow in the spine, pelvic bones, ribs, and area of the shoulders and hips. In addition, groups of myeloma cells cause other cells in the bone called osteoclasts to remove the solid part of the bone and cause soft spots in the bone, resulting in weakened bones and increasing the risk of fractures. Although common, these lesions or other signs of bone loss do not occur in all patients with myeloma.



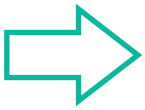
SYMPTOMS

Signs and symptoms of multiple myeloma can vary and, early in the disease, there may be none.

When signs and symptoms do occur, they can include:

- Bone pain, especially in your spine or chest
- Nausea and vomiting
- Constipation
- Loss of appetite
- Mental fogginess or confusion
- Fatigue
- Frequent infections
- Weight loss
- Weakness or numbness in your legs
- Persistent pins and needles in the hands and feet
- Excessive thirst

Make an appointment with your doctor if you have any persistent signs and symptoms that worry you. Any symptom that does not go away or keeps recurring, is an indication to be investigated.



CAUSES

It’s not clear what causes myeloma.

Doctors know that myeloma begins with one or more abnormal plasma cells in your bone marrow – the soft, blood-producing tissue that fills in the center of most of your bones. These abnormal cells then multiply uncontrollably.

Because cancer cells don’t mature and then die as normal cells do, they accumulate, eventually overwhelming the production of healthy cells. In the bone marrow, myeloma cells crowd out healthy white blood cells, red blood cells and platelets, leading to fatigue, an inability to fight infections and abnormal bleeding.

The myeloma cells continue trying to produce antibodies, as healthy plasma cells do, but the myeloma cells produce abnormal antibodies that the body can’t use. Instead, these abnormal antibodies (monoclonal proteins, or M proteins) build up in the body and cause problems such as damage to the kidneys and nerves.

A CONNECTION WITH MGUS

Multiple myeloma often starts out as a relatively benign condition called monoclonal gammopathy of undetermined significance (MGUS).

In the United States, about 3 percent of people older than age 50 have MGUS. Each year, about 1 percent of people with MGUS progress to multiple myeloma or a related cancer.

MGUS, like multiple myeloma, is marked by the presence of M proteins – produced by abnormal plasma cells. However, in MGUS, the levels of M proteins are lower and no damage to the body occurs.

RISK FACTORS

Factors that may increase your risk of multiple myeloma include:

- **Increasing age.** Your risk of multiple myeloma increases as you age, with most people diagnosed in their mid-60s or older.
- **Male sex.** Men are more likely to develop the disease than are women.
- **Black race**. Black people are about twice as likely to develop multiple myeloma as are white people.
- **Family history of multiple myeloma.** If a brother, sister or parent has multiple myeloma, you have an increased risk of the disease.
- **Personal history of a monoclonal gammopathy** of undetermined significance (MGUS) and a single tumor of plasma cells (solitary plasmacytoma)

COMPLICATIONS

Complications of multiple myeloma include:

- **Frequent infections.** Myeloma cells inhibit your body's ability to fight infections.
- **Bone problems.** Multiple myeloma can also affect your bones, leading to bone pain, thinning bones and broken bones.
- **Reduced kidney function.** Multiple myeloma may cause problems with kidney function, including kidney failure. Higher calcium levels in the blood related to eroding bones can interfere with your kidneys' ability to filter your blood's waste. The abnormal proteins produced by the myeloma cells can cause similar kidney problems.
- **Low red blood cell count (anemia).** As myeloma cells crowd out normal blood cells, multiple myeloma can also cause anemia and other blood problems.

DIAGNOSIS

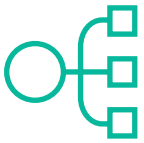
In some cases, your doctor may detect multiple myeloma accidentally when you undergo a blood test for some other condition. In other cases, your doctor may suspect multiple myeloma based on your signs and symptoms especially bone pain.

Tests and procedures used to diagnose multiple myeloma include:

- **Blood tests**. Laboratory analysis of your blood may reveal the M proteins and/or their sub-components called serum free light chains produced by myeloma cells. Another abnormal protein produced by myeloma cells – called beta-2-microglobulin – may be detected in your blood and give your doctor clues about the aggressiveness of your myeloma.

  Additionally, blood tests to examine your kidney function, blood cell counts, calcium levels and uric acid levels can give your doctor clues about your diagnosis.
- **Urine tests**. Analysis of your urine may also show M protein sub-components, which are referred to as Bence Jones proteins when they're detected in urine.
- **Examination of your bone marrow.** Your doctor may remove a sample of bone marrow for laboratory testing. The sample is collected with a long needle inserted into the hip bone (bone marrow aspiration and biopsy).

  In the lab, the sample is examined for myeloma cells. Specialised tests, such as polymerase chain reaction (PCR), fluorescence in situ hybridisation (FISH) and cytogenetics can analyse myeloma cells to understand their genetic abnormalities. Tests are also done to measure the rate at which the myeloma cells are dividing.
- **Imaging tests**. Imaging tests may be recommended to detect bone problems associated with multiple myeloma. Tests may include an X-rays, MRI, CT or positron emission tomography (PET) scans.



ASSIGNING A STAGE AND A RISK CATEGORY

If tests indicate you have multiple myeloma, your doctor will use the information gathered from the diagnostic tests to classify your disease as **stage I**, **stage II** or **stage III**. Stage I indicates less advanced disease, and stage III indicates an advanced disease stage that may affect bone, kidneys and other organs.

Your multiple myeloma may also be assigned a risk category, which indicates the aggressiveness of your disease.

Your multiple myeloma stage and risk category help your doctor understand your prognosis and your treatment options.

TREATMENT

If you're experiencing symptoms, treatment can help relieve pain, control complications of the disease, stabilise your condition and slow the progress of multiple myeloma.

Immediate treatment may not be necessary.

If you have multiple myeloma but aren't experiencing any symptoms (also known as smoldering or indolent multiple myeloma), you may not need treatment. However, your doctor will regularly monitor your condition for signs that the disease is progressing. This may involve periodic blood and urine tests.

If you develop signs and symptoms or your multiple myeloma shows signs of progression, you and your doctor may decide to begin treatment.

TREATMENT OPTIONS

- **Targeted therapy.** Targeted drug treatment focuses on specific abnormalities within cancer cells that allow them to survive. Bortezomib, carfilzomib and ixazomib are drugs that block the final assembly of proteins leading to a build up of unformed proteins . This action causes myeloma cells to die. Targeted-therapy drugs may be administered through a vein in your arm, a subcutaneous injection or in pill form. Other targeted-therapy treatments include monoclonal (synthetic) antibody drugs that bind to the specific proteins present on myeloma cells, causing them to die.
- **Immunomodulatory therapy.** Immunomodulatory drugs use your body's immune system to fight myeloma cells. The drugs thalidomide, lenalidomide and pomalidomide enhance the immune system cells that identify and attack cancer cells. These medications are commonly taken in pill form.
- **Chemotherapy.** Chemotherapy drugs kill growing cells, including myeloma cells. Chemotherapy drugs can be given through a vein in your arm or taken in pill form. High doses of chemotherapy drugs are used before a bone marrow or stem cell transplant.
- **Corticosteroids.** Corticosteroids, such as prednisone and dexamethasone, regulate the immune system to control inflammation in the body. They are also active against myeloma cells. Corticosteroids can be taken in pill form or administered through a vein in your arm.
- **Radiation therapy.** This treatment uses beams of energy, such as X-rays and protons, to damage cancerous myeloma cells and stop their growth. Radiation therapy may be used to quickly shrink myeloma cells in a specific area – for instance, when a collection of abnormal plasma cells form a tumor (plasmacytoma) that's causing pain or destroying a bone.

HOW TREATMENTS ARE USED

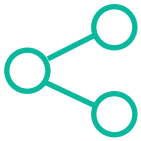
The combination of treatments you're likely to receive will depend on whether you're considered a good candidate for an autologous bone marrow transplant. This depends on the risk of your disease progressing, your age and your overall health.

- If you're considered a **candidate for bone marrow transplant**, your initial therapy will likely include a combination of treatments, such as targeted therapy, immunomodulatory therapy, corticosteroids and, sometimes, chemotherapy.

  Your stem cells will likely be collected after you've undergone a few months of treatment and you have had some reduction in your cancer cells. You may undergo the bone marrow transplant soon after your cells are collected or the transplant may be delayed until after a relapse, if it occurs. In some cases, doctors recommend a tandem (two) bone marrow transplant for people with multiple myeloma.

  After your bone marrow transplant, you'll likely receive targeted therapy or biological therapy as a maintenance treatment to prevent a recurrence of myeloma.
- If you're **not considered a candidate for bone marrow transplant**, your initial therapy will likely include chemotherapy combined with corticosteroids, targeted therapy or biological therapy.
- If your **myeloma recurs or doesn't respond to treatment**, your doctor may recommend repeating another course of the treatment that initially helped you. Another option is trying one or more of the other treatments typically used as first line therapy, either alone or in combination.

  Research on a number of new treatment options is ongoing, and you may be eligible for a clinical trial in order to gain access to those experimental treatments. Talk to your doctor about what clinical trials may be available to you.



TREATING COMPLICATIONS

Because multiple myeloma can cause a number of complications, you may also need treatment for those specific conditions. For example:

- **Bone pain.** Pain medications, radiation therapy and surgery may help control bone pain.
- **Kidney complications.** People with severe kidney damage may need dialysis.
- **Infections.** Your doctor may recommend certain vaccines to prevent infections, such as the flu and pneumonia.
- **Bone loss.** Your doctor may recommend medications called bisphosphonates, such as pamidronate or zoledronic acid, to help prevent bone loss. These drugs reduce the risk of fractures and slow down the growth of myeloma. They are an important adjunct to your therapy.
- **Impaired bone healing.** Warn your dentist if you have myeloma and avoid extractions if possible since myeloma and bisphosphonates impair bone healing.
- **Anemia.** If you have persistent anemia, your doctor may recommend blood transfusions or medications to increase your red blood cell count.

ALTERNATIVE MEDICINE

No alternative medicines have been found to be effective to treat multiple myeloma. But alternative medicine may help you cope with the stress and side effects of myeloma and myeloma treatment.

LENALIDOMIDE ACCESS CHALLENGES IN SOUTH AFRICA

Lenalidomide is used to treat multiple myeloma and some types of myelodysplastic syndromes. Currently there is no cure for multiple myeloma. Stem cell transplants may offer a chance of a cure for myelodysplastic syndromes – although many patients are ineligible for this treatment or unable to access it. Patients with multiple myeloma and myelodysplastic syndromes generally require long-term, ongoing treatment to prevent the progression of their illness.

Lenalidomide provides an important treatment option for many patients with multiple myeloma and myelodysplastic syndromes and should be given for as long as clinical benefits are provided. Lenalidomide is a derivative of older medicine thalidomide but has fewer side effects and is more effective than thalidomide.

Celgene's lenalidomide, sold under the brand name Revlimid, was registered in South Africa in 2016. Prior to the registration of Revlimid, a number of multiple myeloma patients living in South Africa were able to import generic lenalidomide from India for around R4,000 per month via Section 21 authorisations for importation. Following the registration of Celgene's patented product, patients were forced to buy Celgene's patented equivalent at more than R70,000 per month.

Lenalidomide is generally taken for 3 weeks (21 days) – followed by one week off treatment – starting at dosages of 25mgs. In South Africa, a year of 25mg Revlimid treatment costs ZAR 729,288 In India, where generic products are available, a year of 25mg lenalidomide treatment costs ZAR 28,476.

	Revlimid cost in South Africa	Generic lenalidomide costs in India
25 mg capsule	ZAR 3,070 (Celgene)	ZAR 118 (Natco)

Table 1: Costs per capsule

In South Africa, Revlimid is only accessible to patients with private insurance whose insurers are willing to cover the treatment's costs or patients who can cover the costs of treatment out of pocket – often with devastating personal economic implications. The treatment is not provided in the public sector and therefore unavailable to more that 80% of the population who receive care via the public sector.

HOW CELGENE ACQUIRED A MONOPOLY ON LENALIDOMIDE

Lenalidomide is a derivative of the older medicine thalildomide. Thalidomide was first marketed in 1957 as a sedative, although it was taken off the market in 1961 given severe risks to infants when taken during pregnancy. 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. Ongoing research on thalidomide – and its subsequent derivative lenalidomide – demonstrated its efficacy in combating tumours leading Celgene to acquire rights for thalidomide in 1998. In addition to acquiring global rights for thalidomide, Celgene has aggressively pursued patent protection on lenalidomide.

The initial base product patents filed on lenalidomide were filed by Celgene at the international Patent Cooperation Treaty in 1997 and 1998 (PCT/US1997/013375, PCT/US1998/010886). Neither of these patents were filed locally in South Africa. However, Celgene has subsequently filed 32 secondary patents related to lenalidomide that could inhibit use of generics in South Africa until 2028. An additional six patents filed at the Patent Cooperation Treaty could further extend patent barriers on lenalidomide (and the use of biomarkers and genes to inform treatment) until 2036 if granted in South Africa. See Table 2 on the next page.

Table 2: Patents granted on lenalidomide in South Africa

2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036
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**Renewal payments not up to date*

In our research, we identified multiple granted and abandoned patents on which renewal fees have not been paid. As patent statuses may change, we have used current patent statuses from the Companies and Intellectual Property Commission online patent database sourced on 25 May 2018 and noted when data regarding the payment of renewals fees is not up to date.

The vast majority of patents identified were granted on methods of use of lenalidomide, including unapproved indications. In cross-checking patent's granted in South Africa with matching applications sought in other jurisdictions on WIPO's patent scope database, we found that for all patents granted on lenalidomide in South Africa a matching patent application (or divisional application thereof) was withdrawn or rejected in at least one other jurisdiction. In other words, many patents granted in South Africa were not granted in other jurisdictions or granted for a smaller scope of protection following amendments requested by the relevant jurisdiction's patent office.

With the adoption of stricter patentability criteria in South Africa and substantive patent examination and opposition procedures as recommended by Fix the Patent Laws, it is likely that many patents granted on lenalidomide in South Africa would have been rejected or amended as seen in other jurisdictions – allowing for earlier access to more affordable generic products in South Africa.

WHAT ABOUT THALIDOMIDE?

While research has demonstrated that lenalidomide is more effective and has fewer side-effects than thalidomide, thalidomide can be used to treat multiple myeloma and myelodysplastic syndromes in situations where lenalidomide is unavailable.

However, thalidomide is not currently available in South Africa's public sector and can only be accessed via the private sector. Thalidomide is not included on South Africa's Tertiary and Quaternary Essential Medicines List which would require its availability in the public sector due to cost.

In South Africa, only Celgene's thalidomide product is currently available at a cost of ZAR 132 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 192,720. Equivalent generic products are available in India for less that R10,000 for a year's treatment.

Celgene filed two patents on methods and compositions using thalidomide in South Africa in 2006 (2006/29227, 2006/03718). Patent 2006/29227 remains pending, whereas patent 2006/03718 was granted but does not have available information regarding the payment of renewal fees.

Until a generic company seeks to launch a competitor product it is unclear whether Celgene will seek to claim monopoly on this medicine. However, as thalidomide is more than 60 years old, any monopoly claims made by Celgene should be vigorously challenged.

IN LOVING MEMORY OF SUE JOHNSON
(04/04/1954 – 16/05/2018)

It is with immense sadness that the Fix the Patent Laws (FTPL) Coalition shared the news of the passing of a dear friend and brave patient advocate, Sue Johnson, during May 2018. Sue was a mother of two children and grandmother to two girls. She was born in the UK and moved to South Africa in 1983, where she spent her life working for the UN and Habitat for Humanity in Cape Town until her retirement in 2017.

Sue was also a prominent patient advocate for access to lenalidomide – a medicine prescribed for multiple myeloma – for the Cancer Alliance and FTPL. She spoke bravely and passionately of the struggles she face in accessing the medicine she needed at an affordable price, most memorably at the stakeholder meetings hosted by the Department of Trade and Industry on Intellectual Property Reform in October 2017 and at the Cancer Alliance launch of the Access to Medicine campaign in January 2018.

Sue was diagnosed with breast cancer in 2008 and with Multiple myeloma in 2014. While she was initially able to access a generic lenalidomide treatment from India on a Section 21 authorisation from the Medicines Control Council at a price of about R5000 per month, this was revoked in 2016 when the originator product from Celgene, Revlimid, was registered in South Africa, at a cost of R882,000 per year. Sue's medical insurer agreed to cover the increased cost of nearly R75,000 per month – but only for four months. After that, Sue and her family had to struggle to get the rest from their own pockets.

Secondary patents may block more affordable generics from entering the South African market until at least 2028. This means that equitable access for patients like Sue is a long way off.

As Sue recalled: “I remember that day very well, when everything changed: one day I had the support of the MCC and was able to import my medication from India. The next day the MCC took away my authorisation and my right to access generic medication. The registration of the patented product changed everything for me with just the stroke of a pen. Overnight I could no longer afford the treatment I needed to live.”

Sue will be remembered by all for her bravery and unselfish desire to fight for equitable and affordable access for all – despite knowing that she might not be able to benefit from it.

FTPL salutes Sue and will continue the fight for equitable and affordable access to lifesaving medicines for all in South Africa in her memory.

METHODOLOGY AND DISCLAIMER

This document provides an updated patent landscape for lenalidomide and thalidomide in South Africa. The previous patent landscape published by the Cancer Alliance for these medicines in October 2017[i] has been updated to reflect additional patents identified on lenalidomide in a White Paper published by I-MAK in October 2017[ii]. I-MAK's research revealed 105 filed, granted and abandoned patents sought by Celgene Corporation on lenalidomide in the United States.

Using patent data supplied by I-MAK, we updated our patent landscape to include previously unidentified filed, granted and abandoned patents in South Africa.

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. Patent statuses may also change. All patent statuses included in this updated landscape were sourced from the Companies and Intellectual Property Commission and Wipo's Patent scope online patent databases on 25 May 2018.

i. https://www.canceralliance.co.za/important-new-report-on-patent-barriers-to-cancer-treatment-in-sa-released/
ii. http://www.i-mak.org/americas-overspend/

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- American Cancer Society https://www.cancer.org
- National Cancer Registry. Cancer incidence for South Africa. 2014. www.ncr.ac.za

ANNEXURE 1

LENALIDOMIDE PATENTS IN SOUTH AFRICA

PATENT TITLE	PATENT HOLDER	CIPC NUMBER	PCT NUMBER	INTERNATIONAL FILING DATE	LODGING DATE	EXPIRY DATE	STATUS	ACTIONS ON MATCHING APPLICATIONS OR DIVISIONAL PATENT APPLICATIONS THEREOF IN OTHER JURISDICTIONS	CATEGORY
ISOINDOLE-IMIDE COMPOUNDS COMPOSITIONS AND USES THEREOF	Celgene Corporation	2003/05759	PCT/ US01/50401	21-Dec-2001	25-Jul-2003	21-Dec-2021	Granted (Renewal payments up to 2015)	Withdrawn in Europe (EP2168958, EP1767533). Refused in Czechia (PV2005-714)	Secondary: Markush
MODULATION OF STEM AND PROGENITOR CELL DIFFERENTIATION ASSAYS AND USES THEREOF	Celgene Corporation	2004/08367	PCT/ US03/11327	13-Apr-2003	15-Oct-2004	13-Apr-2023	Granted (Renewal payments up to date)	Withdrawn (1020157019734, 1020127026446) and refused (1020117029329) in South Korea	Secondary: Method of Action
MODULATION OF STEM AND PROGENITOR CELL DIFFERENTIATION ASSAYS AND USES THEREOF	Celgene Corporation	2004/08368	PCT/ US03/011190	11-Apr-2003	15-Oct-2004	11-Apr-2023	Granted (Renewal payments up to date)	Withdrawn in Europe (EP1538913)	Secondary: Method of Action
METHODS FOR IDENTIFICATION OF MODULATORS OF ANGIOGENESIS COMPOUNDS DISCOVERED THEREBY AND METHODS OF TREATMENT USING THE COMPOUNDS	Celgene Corporation	2004/08369	PCT/ US03/011578	14-Apr-2003	15-Oct-2004	14-Apr-2023	Lapsed (Due to non-payment of renewals)	Withdrawn in Europe (EP1496878)	Secondary: Method of Action
METHODS AND COMPOSITIONS USING SELECTIVE CYTOKINE INHIBITORY DRUGS FOR TREATMENT AND MANAGEMENT OF CANCERS AND OTHER DISEASES	Celgene Corporation	2004/09387	PCT/ US03/15468	16-May-2003	22-Nov-2004	16-May-2023	Granted (Renewals paid up to 2014)	Withdrawn Europe (EP1556033, EP2258363)	Secondary: Method of Use
METHODS AND COMPOSITIONS USING IMMUNOMODULATORY COMPOUNDS FOR TREATMENT AND MANAGEMENT OF CANCERS AND OTHER DISEASES	Celgene Corporation	2004/09388	PCT/ US03/15470	16-May-2003	22-Nov-2004	16-May-2023	Granted (Renewal payments up to date)	Withdrawn in Europe (EP2272512, EP2087891, EP2105136, EP2316455, EP2272513, EP2561874) Refused in South Korea (1020077001593)	Secondary: Method of Use

PATENT TITLE	PATENT HOLDER	CIPC NUMBER	PCT NUMBER	INTERNATIONAL FILING DATE	LODGING DATE	EXPIRY DATE	STATUS	ACTIONS ON MATCHING APPLICATIONS OR DIVISIONAL PATENT APPLICATIONS THEREOF IN OTHER JURISDICTIONS	CATEGORY
METHODS OF USING AND COMPOSITIONS COMPRISING IMMUNOMODULATORY COMPOUNDS FOR THE TREATMENT AND MANAGEMENT OF MYELODYSPLASTIC SYNDROMES	Celgene Corporation	2005/03025	PCT/ US03/011323	13-Apr-2003	14-Apr-2005	13-Apr-2023	Granted (Renewal payments up to date)	Withdrawn in Europe (EP1900369) Refused in South Korea (1020077001593)	Secondary: Method of Use
METHODS OF USING AND COMPOSITIONS COMPRISING IMMUNOMODULATORY COMPOUNDS FOR TREATMENT, MODIFICATION AND MANAGEMENT OF PAIN	Celgene Corporation	2005/03240	PCT/ US03/033757	24-Oct-2003	21-Apr-2005	24-Oct-2023	Lapsed (Due to non-payment of renewals)	Withdrawn in Europe (EP1556044) Refused in South Korea (1020057007000)	Secondary: Method of Use (Unapproved indication)
METHODS OF USING AND COMPOSITIONS COMPRISING SELECTIVE CYTOKINE INHIBITORY DRUGS FOR TREATMENT, MODIFICATION AND MANAGEMENT OF PAIN	Celgene Corporation	2005/03241	PCT/ US03/034005	24-Oct-2003	21-Apr-2005	24-Oct-2023	Lapsed (Due to non-payment of renewals)	Withdrawn in Europe (EP2036553, EP1562586)	Secondary: Method of Use (Unapproved indication)
METHODS OF USING AND COMPOSITIONS COMPRISING SELECTIVE CYTOKINE INHIBITORY DRUGS FOR TREATMENT AND MANAGEMENT OF MACULAR DEGENERATION	Celgene Corporation	2005/03468	PCT/ US03/034535	31-Oct-2003	29-Apr-2005	31-Oct-2023	Granted (Renewals paid up to 2015)	Withdrawn in Europe (EP1567148)	Secondary: Method of Use (Unapproved indication)
METHODS AND COMPOSITIONS USING SELECTIVE CYTOKINE INHIBITORY DRUGS FOR TREATMENT AND MANAGEMENT OF CANCERS AND OTHER DISEASES	Celgene Corporation	2005/03655	PCT/ US03/035545	06-Nov-2003	06-May-2005	06-Nov-2023	Granted (No renewal payment info)	Withdrawn in Europe (EP1567154) Refused in South Korea (1020097008255)	Secondary: Method of Use
METHODS FOR TREATMENT AND MANAGEMENT OF BRAIN CANCER USING 1-Oxo-2-(2,6-DIOXOPIPERIDIN-3-YL)-4-METHYLISOINDOLINE	Celgene Corporation	2005/03656	PCT/ US03/035544	06-Nov-2003	06-May-2005	06-Nov-2023	Granted (Renewal payments up to 2016)	Withdrawn in Europe (EP1567158)	Secondary: Method of Use (Unapproved indication)

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METHODS OF USING AND COMPOSITIONS COMPRISING IMMUNOMUDULATORY COMPOUNDS FOR THE TREATMENT AND MANAGEMENT OF MYELOPROLIFERATIVE DISEASES	Celgene Corporation	2005/03666	PCT/ US03/011328	13-Apr-2003	06-May-2005	13-Apr-2023	Granted (Renewal payment up to 2016)	Withdrawn in Europe (EP2210606)	Secondary: Method of Use (Unapproved indication)
METHODS FOR TREATING CANCERS USING POLYMORPHIC FORMS OF 3-(4-AMINO- 1,3DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE -2,6- DIONE	Celgene Corporation	2005/09232	PCT/ US04/014004	05-May-2004	15-Nov-2005	05-May-2024	Granted (Renewal payments up to 2015))	Withdrawn in Europe (EP2460522, EP1635826) and the Philippines (12005502068) Refused in Colombia (05125373	Secondary: Method of Use
POLYMORPHIC-FORMS OF 3-(4-AMINO-1-OXO-1,3DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6- DIONE	Celgene Corporation	2006/01858	PCT/ US04/028736	03-Sep-2004	03-Mar-2006	03-Sep-2024	Granted (Renewal payments up to date)	Withdrawn in Europe (EP2425836) Withdrawn in South Korea (1020087012598) Refused in Colombia (06023144)	Secondary: Polymorphic form
METHODS OF USING AND COMPOSITIONS COMPRISING IMMUNOMODULATORY COMPOUNDS FOR TREATMENT, MODIFICATION AND MANAGEMENT OF PAIN	Celgene Corporation	2006/03401	PCT/ US04/012721	23-Apr-2004	28-Apr-2006	23-Apr-2024	Lapsed (Due to non-payment of renewals)	Withdrawn in Europe (EP1680111) and South Korea (1020067009894)	Secondary: Method of Use (Unapproved indication)
METHODS OF USING AND COMPOSITIONS COMPRISING SELECTIVE CYTOKINE INHIBITORY DRUGS FOR TREATMENT, MODIFICATION AND MANAGEMENT OF PAIN	Celgene Corporation	2006/03461	PCT/ US04/012722	23-Apr-2004	02-May-2006	23-Apr-2024	Lapsed (Due to non-payment of renewals)	Withdrawn in Europe (EP1679967) Refused in South Korea (1020067009895)	Secondary: Method of Use (Unapproved indication)
COMPOSITION AND METHOD FOR TREATING MACULAR DEGENERATION	Celgene Corporation	2006/03462	PCT/ US04/013252	28-Apr-2004	02-May-2006	28-Apr-2024	Lapsed (Due to non-payment of renewals)	Withdrawn in South Korea (1020067010463) and Europe (EP1684743)	Secondary: Method of Use (Unapproved indication)

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METHODS OF USING AND COMPOSITIONS COMPRISING IMMUNOMODULATORY COMPOUNDS FOR THE TREATMENT AND MANAGEMENT OF ASBESTOS-RELATED DISEASES AND DISORDERS	Celgene Corporation	2006/03720	PCT/ US04/037085	04-Nov-2004	10-May-2006	04-Nov-2024	Lapsed (Due to non-payment of renewals)	Withdrawn in South Korea (1020067011016) and Europe (EP1689223)	Secondary: Method of Use (Unapproved indication)
METHODS AND COMPOSITIONS FOR THE TREATMENT AND MANAGEMENT OF HEMOGLOBINOPATHY AND ANEMIA	Celgene Corporation	2006/04815	PCT/ US04/040226	02-Dec-2004	12-Jun-2006	02-Dec-2024	Granted (Renewal payments up to 2015)	Withdrawn in Germany (null) and Europe (EP1694328). Refused (1020067013289, 1020127006117, 1020117021413) in South Korea	Secondary: Method of Use (Unapproved indication)
IMMUNOMODULATORY COMPOUNDS FOR THE TREATMENT OF CENTRAL NERVOUS SYSTEM DISORDERS	Celgene Corporation	2006/05475	PCT/ US04/043924	27-Dec-2004	03-Jul-2006	27-Dec-2024	Lapsed (Due to non-payment of renewals)	Withdrawn in Germany (null) and Europe (EP1705988). Refused n South Korea (1020067015162)	Secondary: Method of Use (Unapproved indication)
METHODS OF USING AND COMPOSITIONS COMPRISING IMMUNOMODULATORY COMPOUNDS FOR TREATMENT AND MANAGEMENT OF SKIN DISEASES OR DISORDERS	Celgene Corporation	2006/07799	PCT/ US05/008999	18-Mar-2005	18-Sep-2006	18-Mar-2025	Granted (Renewal payments up to 2015)	Withdrawn in Germany (null) and Europe (EP2505200, EP1737453)	Secondary: Method of Use (Unapproved indication)
METHODS AND COMPOSITIONS FOR THE TREATMENT, PREVENTION OR MANAGEMENT OF DYSFUNTIONAL SLEEP AND DYSFUNCTIONAL SLEEP ASSOCIATED WITH DISEASE	Celgene Corporation	2006/08568	PCT/ US05/010937	31-Mar-2005	13-Oct-2006	31-Mar-2025	Lapsed (Due to non-payment of renewals)	Withdrawn in Germany (null), Europe (EP1740178) and South Korea (1020067022827)	Secondary: Method of Use (Unapproved indication)
METHODS OF USING AND COMPOSITIONS COMPRISING IMMUNOMODULATORY COMPOUNDS FOR THE TREATMENT AND MANAGEMENT OF PULMONARY HYPERTENSION	Celgene Corporation	2006/09226	PCT/ US05/013598	21-Apr-2005	06-Nov-2006	21-Apr-2025	Lapsed (Due to non-payment of renewals)	Withdrawn in Germany (null), Europe (EP1755600) and South Korea (1020067024523)	Secondary: Method of Use (Unapproved indication)

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PROCESSES FOR THE PREPARATION OF SUBSTITUTED 2-(2,6-DIOXOPIPERIDIN-3-YL)-1- OXOISOINDOLINES	Celgene Corporation	2007/02382	PCT/US05/031318	31-Aug-2005	22-Mar-2007	31-Aug-2025	Granted (No info re renewal payments)	Withdrawn in South Korea (1020077007538)	Secondary: Process
METHODS AND COMPOSITIONS USING IMMUNOMODULATORY COMPOUNDS FOR TREATMENT AND MANAGEMENT OF CENTRAL NERVOUS SYSTEM INJURY	Celgene Corporation	2007/04890	PCT/US05/042331	18-Nov-2005	18-Jul-2007	18-Nov-2025	Lapsed (Due to non-payment of renewals)	Withdrawn in Europe (EP1827431) and South Korea (1020077014355)	Secondary: Method of Use (Unapproved indication)
METHODS AND COMPOSITIONS USING IMMUNOMODULATORY COMPOUNDS FOR THE TREATMENT OF IMMUNODEFICIENCY DISORDERS	Celgene Corporation	2007/04964	PCT/US05/043360	30-Nov-2005	27-Jun-2007	30-Nov-2025	Lapsed (Due to non-payment of renewals)	Withdrawn in South Korea (1020077015076)	Secondary: Method of Use (Unapproved indication)
ISOINDOLE-MIDE COMPOUNDS AND COMPOSITIONS COMPRISING AND METHODS OF USING THE SAME	Celgene Corporation	2008/02490	PCT/US06/033278	25-Aug-2006	18-Mar-2008	25-Aug-2026	Lapsed (Due to non-payment of renewals)	Withdrawn in Germany (null) and South Korea (null)	Secondary: Metabolites, Prodrugs, Derivatives, Compositions
METHODS USING 3-(4-AMINO-1-OXO-1,3- DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6- DIONE FOR TREATMENT OF CERTAIN LEUKEMIAS	Celgene Corporation	2008/03700	PCT/US06/038844	03-Oct-2006	29-Apr-2008	03-Oct-2026	Granted (Renewal payments up to date)	Refused (EP1931343) and withdrawn (EP2526946) in Europe. Withdrawn (1020147014746) and refused (1020167023898, 1020087010897) in South Korea. Refused in Colombia (08044733)	Secondary: Method of Use (Unapproved indication)
METHODS AND COMPOSITIONS USING IMMUNOMODULATORY COMPOUNDS IN COMBINATION THERAPY	Celgene Corporation	2008/09956	PCT/US07/012495	24-May-2007	28-Nov-2008	24-May-2027	Granted (No renewal payment info)	Withdrawn in South Korea (1020087031357) and Europe (EP2023912)	Secondary: Combinations
4'-O-SUBSTITUTED ISOINDOLINE DERIVATIVES AND COMPOSITIONS COMPRISING AND METHODS OF USING THE SAME	Celgene Corporation	2009/06497	PCT/US08/003602	19-Mar-2008	17-Sep-2009	19-Mar-2028	Granted (Renewal payments up to date)	Refused in Colombia (09106869) and South Korea (1020177021704)	Secondary: Metabolites, Prodrugs, Derivatives, Compositions

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USE OF IMMUNOMODULATORY COMPOUNDS FOR THE TREATMENT OF DISORDERS ASSOCIATED WITH ENDOTHELIAL DYSFUNCTION	Celgene Corporation	2010/03115	PCT/ US08/012537	07-Nov-2008	04-May-2010	07-Nov-2028	Granted (Renewal payments up to 2014)	Withdrawn in Europe (EP2219627)	Secondary: Method of Use (Unapproved indication)
SOLID FORMS COMPRISING 3-(4-AMINO-1- OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE- 2,6-DIONE AND A COFORMER, COMPOSITIONS AND METHODS OF USE THEREOF	Celgene Corporation	Designated state for national filing	PCT/ US2016/053900	25-Mar-2014	N/A	25-Mar-2034	Not filed to date	N/A	Secondary: Crystalline forms, Composition
METHODS FOR TREATING CHRONIC LYMPHOCYTIC LEUKEMIA AND THE USE OF BIOMARKERS AS A PREDICTOR OF CLINICAL SENSITIVITY TO IMMUNOMODULATORY THERAPIES	Celgene Corporation	Designated state for national filing	PCT/ US2016/045320	03-Aug-2016	N/A	03-Aug-2036	Not filed to date	N/A	Gene or biomarker testing to inform treatment
METHODS FOR TREATING SOLID TUMORS AND THE USE OF BIOMARKERS AS A PREDICTOR OF CLINICAL SENSITIVITY TO IMMUNOMODULATORY THERAPIES	Celgene Corporation	Designated state for national filing	PCT/ US2016/046490	11-Aug-2016	N/a	11-Aug-2036	Not filed to date	N/A	Gene or biomarker testing to inform treatment
METHODS FOR TREATING DIFFUSE LARGE B- CELL LYMPHOMA AND THE USE OF BIOMARKERS AS A PREDICTOR OF RESPONSIVENESS TO DRUGS	Celgene Corporation	Designated state for national filing	PCT/ US2016/053092	22-Sep-2016	N/A	22-Sep-2036	Not filed to date	N/A	Gene or biomarker testing to inform treatment
COMBINATION THERAPY FOR TREATMENT OF HEMATOLOGICAL CANCERS AND SOLID TUMORS	Celgene Corporation	Designated state for national filing	PCT/ US2016/053900	27-Sep-2016	N/A	27-Sep-2036	Not filed to date	N/A	Secondary: Combinations
METHODS FOR THE IDENTIFICATION, EVALUATION AND TREATMENT OF PATIENTS HAVING MULTIPLE MYELOMA	Celgene Corporation, Millennium Pharmaceuticals	Designated state for national filing	PCT/ US2016/060552	04-Nov-2016	N/A	24-Nov-2036	Not filed to date	N/A	Gene or biomarker testing to inform treatment

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