[Template:Drugbox](/wiki/Template:Drugbox" \o "Template:Drugbox) **Thalidomide** sold under the brand names **Immunoprin**, among others, is an [immunomodulatory drug](/wiki/Immunotherapy) and the prototype of the [thalidomide class of drugs](/wiki/Discovery_and_development_of_thalidomide_and_its_analogs). Today, thalidomide is used mainly as a treatment of certain cancers ([multiple myeloma](/wiki/Multiple_myeloma)) and of a complication of [leprosy](/wiki/Leprosy).

Thalidomide was first marketed in 1957 in West Germany under the trade-name **Contergan**. The German drug company [Chemie Grünenthal](/wiki/Grünenthal) developed and sold the drug. Primarily prescribed as a [sedative](/wiki/Sedative) or [hypnotic](/wiki/Hypnotic), thalidomide also claimed to cure "[anxiety](/wiki/Anxiety), [insomnia](/wiki/Insomnia), [gastritis](/wiki/Gastritis), and tension".[[1]](#cite_note-1) Afterwards, it was used against [nausea](/wiki/Nausea) and to alleviate [morning sickness](/wiki/Morning_sickness) in pregnant women. Thalidomide became an [over-the-counter](/wiki/Over_the_counter) drug in West Germany on October 1, 1957. Shortly after the drug was sold in West Germany, between 5,000 and 7,000 infants were born with [phocomelia](/wiki/Phocomelia) (malformation of the limbs). Only 40% of these children survived.[[2]](#cite_note-2) Throughout the world, about 10,000 cases were reported of infants with phocomelia due to thalidomide; only 50% of the 10,000 survived. Those subjected to thalidomide while in the womb experienced limb deficiencies in a way that the long limbs either were not developed or presented themselves as stumps. Other effects included deformed eyes and hearts, deformed alimentary and urinary tracts, blindness and deafness.[[3]](#cite_note-3) The negative effects of thalidomide led to the development of more structured drug regulations and control over drug use and development.[[4]](#cite_note-4)[Template:TOC limit](/wiki/Template:TOC_limit)

## Contents

* 1 Medical uses[[edit](/index.php?title=(none)&action=edit&section=1)]
* 2 Adverse effects[[edit](/index.php?title=(none)&action=edit&section=2)]
  + 2.1 Carcinogenicity[[edit](/index.php?title=(none)&action=edit&section=3)]
  + 2.2 Contraindications[[edit](/index.php?title=(none)&action=edit&section=4)]
  + 2.3 Interactions[[edit](/index.php?title=(none)&action=edit&section=5)]
  + 2.4 Overdose[[edit](/index.php?title=(none)&action=edit&section=6)]
* 3 Mechanism of action[[edit](/index.php?title=(none)&action=edit&section=7)]
  + 3.1 Cereblon[[edit](/index.php?title=(none)&action=edit&section=8)]
  + 3.2 Leprosy treatment[[edit](/index.php?title=(none)&action=edit&section=10)]
  + 3.3 Cancer treatment[[edit](/index.php?title=(none)&action=edit&section=11)]
* 4 Thalidomide analogs[[edit](/index.php?title=(none)&action=edit&section=12)]
* 5 Society and culture[[edit](/index.php?title=(none)&action=edit&section=13)]
  + 5.1 Regulatory approved uses[[edit](/index.php?title=(none)&action=edit&section=14)]
  + 5.2 Birth defects crisis[[edit](/index.php?title=(none)&action=edit&section=15)]
  + 5.3 Aftermath of scandal[[edit](/index.php?title=(none)&action=edit&section=16)]
    - 5.3.1 Germany[[edit](/index.php?title=(none)&action=edit&section=17)]
    - 5.3.2 United Kingdom[[edit](/index.php?title=(none)&action=edit&section=18)]
    - 5.3.3 Australia[[edit](/index.php?title=(none)&action=edit&section=19)]
    - 5.3.4 Canada[[edit](/index.php?title=(none)&action=edit&section=20)]
    - 5.3.5 United States[[edit](/index.php?title=(none)&action=edit&section=21)]
  + 5.4 Notable people affected[[edit](/index.php?title=(none)&action=edit&section=22)]
  + 5.5 Change in drug regulations[[edit](/index.php?title=(none)&action=edit&section=23)]
* 6 Research[[edit](/index.php?title=(none)&action=edit&section=24)]
* 7 See also[[edit](/index.php?title=(none)&action=edit&section=25)]
* 8 References[[edit](/index.php?title=(none)&action=edit&section=26)]
* 9 Further reading[[edit](/index.php?title=(none)&action=edit&section=27)]
* 10 External links[[edit](/index.php?title=(none)&action=edit&section=28)]

## Medical uses[[edit](/index.php?title=(none)&action=edit&section=1)]

[thumb|Pack of Thalidomide tablets](/wiki/File:Pack_of_Thalidomide_tablets_c.1960.JPG) Thalidomide is used for a number of conditions including [erythema nodosum leprosum](/wiki/Erythema_nodosum_leprosum), [multiple myeloma](/wiki/Multiple_myeloma) (in combination with [dexamethasone](/wiki/Dexamethasone)), and various other [cancers](/wiki/Cancers), for some symptoms of [HIV/AIDS](/wiki/HIV/AIDS), [Crohn's disease](/wiki/Crohn's_disease), [sarcoidosis](/wiki/Sarcoidosis), [graft-versus-host disease](/wiki/Graft-versus-host_disease), [rheumatoid arthritis](/wiki/Rheumatoid_arthritis) and a number of skin conditions that have not responded to usual treatment.<ref name=AHFS>[Template:Cite web](/wiki/Template:Cite_web)</ref>

The bacterium that causes [tuberculosis](/wiki/Tuberculosis) is related to leprosy. Thalidomide may be helpful in some cases where [standard TB drugs](/wiki/Tuberculosis_management) and [corticosteroids](/wiki/Corticosteroids) are not sufficient to resolve severe inflammation in the brain.[[5]](#cite_note-5)[[6]](#cite_note-6) There is no conclusive evidence that thalidomide or [lenalidomide](/wiki/Lenalidomide) is useful to bring about or maintain remission in Crohn's disease.[[7]](#cite_note-7)[[8]](#cite_note-8)

## Adverse effects[[edit](/index.php?title=(none)&action=edit&section=2)]

Thalidomide may cause side effects, such as [polyneuropathy](/wiki/Polyneuropathy), fatigue, skin rash, and [venous thromboembolism (VTE)](/wiki/Venous_thromboembolism), or blood clots, which could lead to [stroke](/wiki/Stroke) or [myocardial infarction](/wiki/Myocardial_infarction).[[9]](#cite_note-9)[[10]](#cite_note-10) **Adverse effects by frequency:**<ref name = DM>[Template:Cite web](/wiki/Template:Cite_web)</ref><ref name = MSR>[Template:Cite web](/wiki/Template:Cite_web)</ref><ref name = EMC>[Template:Cite web](/wiki/Template:Cite_web)</ref><ref name = TGA>[Template:Cite web](/wiki/Template:Cite_web)</ref>  
**Very common (may affect more than 1 in 10 people):** [Template:Colbegin](/wiki/Template:Colbegin)

* Somnolence (drowsiness; ~40%)
* [Edema](/wiki/Edema) (~60%)
* Hypotension (low blood pressure)
* Headache
* Haematuria (blood in the urine)
* Arthralgia (joint pain)
* Myalgia (muscle aches)
* Increased bilirubin
* [Neutropenia](/wiki/Neutropenia) (~30%)
* [Leucopenia](/wiki/Leucopenia) (~15-40%)
* [Lymphopenia](/wiki/Lymphopenia)
* Constipation
* [Peripheral neuropathy](/wiki/Peripheral_neuropathy)†
* Dizziness
* [Paraesthesia](/wiki/Paraesthesia)
* [Dysaesthesia](/wiki/Dysaesthesia)

[Template:Colend](/wiki/Template:Colend)

**Common (may affect up to 1 in 10 people):** [Template:Colbegin](/wiki/Template:Colbegin)

* Pulmonary embolism
* Vomiting
* Dry mouth
* Toxic skin eruption
* Dry skin
* Rash
* Urticaria (hives)
* Pyrexia (fever)
* Asthenia
* [Interstitial lung disease](/wiki/Interstitial_lung_disease)
* Heart failure
* Depression
* [Pneumonia](/wiki/Pneumonia)

[Template:Colend](/wiki/Template:Colend)

**Uncommon (may affect up to 1 in 100 people):**

* Shortness of breath
* Tremor

**Rare (may affect up to 1 in 1,000 people):** [Template:Colbegin](/wiki/Template:Colbegin)

* Increased appetite
* Bradycardia (low heart rate)
* Tachycardia (high heart rate)
* Cardiac arrhythmia
* Malaise
* Deep vein thrombosis

[Template:Colend](/wiki/Template:Colend)

**Very rare (may affect up to 1 in 10,000 people):** [Template:Colbegin](/wiki/Template:Colbegin)

* [Thrombocytopenia](/wiki/Thrombocytopenia)
* Anaemia
* [Hypothyroidism](/wiki/Hypothyroidism)
* Reduced libido
* Confusion
* Seizures
* Orthostatic hypotension
* Thromboembolic events
* Bronchospasm
* Intestinal obstruction
* Pruritus (itchiness)
* [Stevens-Johnson syndrome](/wiki/Stevens-Johnson_syndrome)
* [Toxic epidermal necrolysis](/wiki/Toxic_epidermal_necrolysis)
* Facial oedema
* Photosensitivity (light sensitivity)
* Menstruation abnormalities

[Template:Colend](/wiki/Template:Colend)

† Peripheral neuropathy may be irreversible and usually results from chronic (usually a matter of months) exposure to thalidomide.<ref name = EMC/>

### Carcinogenicity[[edit](/index.php?title=(none)&action=edit&section=3)]

Animal studies did not demonstrate any [carcinogenicity](/wiki/Carcinogen) even when rats and mice were exposed to up to 11 times the therapeutic dose of thalidomide.<ref name = TGA/> Despite this there have been some concerns that it may cause secondary malignancies in patients with multiple myeloma. The FDA has issued a statement that it is investigating these concerns.[[11]](#cite_note-11) Some clinical trials have supported this claim and the major secondary malignancy that thalidomide is associated with is [acute myeloid leukaemia](/wiki/Acute_myeloid_leukaemia).[[12]](#cite_note-12) The [MHRA](/wiki/Medicines_and_Healthcare_products_Regulatory_Agency) of the [UK](/wiki/United_Kingdom) and [Health Canada](/wiki/Health_Canada) of [Canada](/wiki/Canada) have also issued warnings to healthcare professionals regarding the risk of secondary malignancies due to thalidomide exposure.[[13]](#cite_note-13)[[14]](#cite_note-14)

### Contraindications[[edit](/index.php?title=(none)&action=edit&section=4)]

Contraindications include:<ref name = TGA/>

* Known hypersensitivity to thalidomide
* Pregnancy or breastfeeding
* Patient age < 12 years
* Patients who are unable or unwilling to comply with required contraceptive measures

### Interactions[[edit](/index.php?title=(none)&action=edit&section=5)]

There are no expected [pharmacokinetic](/wiki/Pharmacokinetics) interactions between thalidomide and other medicines due to its neutral effects on p-glycoprotein and P450 cytochromes.<ref name = TGA/> It may interact with sedatives due to its sedative action.<ref name = TGA/> It may also interact with bradycardic agents due to its bradycardia-inducing effects.<ref name = TGA/> The risk of peripheral neuropathy may be increased by concomitant treatment with other agents known to cause peripheral neuropathy.<ref name = TGA/> The risk of venous thromboembolisms with thalidomide seems to be increased when patients are treated with oral contraceptives or other cytotoxic agents (including doxorubicin and melphalan) concurrently.<ref name = TGA/> Thalidomide may interfere with the contraceptive effects of various contraceptives and hence it is advised that women of reproductive age use at least two different means of contraception to ensure that no child will be conceived while they are receiving thalidomide.<ref name = TGA/>

### Overdose[[edit](/index.php?title=(none)&action=edit&section=6)]

Eighteen cases of overdoses have been reported to date with doses of up to 14.4 g without any reported fatalities.<ref name = TGA/> No specific antidote for overdoses exists and treatment is purely supportive.<ref name = TGA/>

## Mechanism of action[[edit](/index.php?title=(none)&action=edit&section=7)]

The precise mechanism of action for thalidomide is unknown, but possible mechanisms include anti-angiogenic and oxidative stress-inducing effects.<ref name = mech>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> It also inhibits [TNF-α](/wiki/Tumor_necrosis_factor_alpha), [IL-6](/wiki/Interleukin_6), [IL-10](/wiki/Interleukin_10) and [IL-12](/wiki/Interleukin_12) production,<ref name = mech2>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> modulates the production of [IFN-γ](/wiki/Interferon_gamma)<ref name = mech2/> and enhances the production of [IL-2](/wiki/Interleukin_2), [IL-4](/wiki/Interleukin_4) and [IL-5](/wiki/Interleukin_5) by immune cells.<ref name = mech2/> It increases lymphocyte count, costimulates T cells and modulates [natural killer cell](/wiki/Natural_killer_cell) cytotoxicity.<ref name = mech2/> It also inhibits [NF-κB](/wiki/NF-κB) and [COX-2](/wiki/Cyclooxygenase_2) activity.<ref name = mech/>

In 1990, a group of researchers in Brazil noted that [TNF alpha](/wiki/TNF_alpha) levels went up in leprosy reactional states and observed that TNF levels decreased in some patients on treatment with thalidomide, hence potentially explaining the efficacy of thalidomide in treating ENL.[[15]](#cite_note-15) The mechanism of thalidomide's [teratogenic](/wiki/Teratology) action has led to over 2000 research papers and the proposal of 15 or 16 plausible mechanisms.[[16]](#cite_note-16) [Angiogenesis](/wiki/Angiogenesis) is critical during limb development of the foetus. Thalidomide can directly inhibit angiogenesis induced by bFGF or VEGF *in vivo*.[[17]](#cite_note-17) Teratogenic analogs inhibit angiogenesis whereas nonteratogenic analogs do not inhibit angiogenesis.[[17]](#cite_note-17) In 2009, research by other groups confirmed "conclusively that loss of newly formed blood vessels is the primary cause of thalidomide teratogenesis, and developing limbs are particularly susceptible because of their relatively immature, highly angiogenic vessel network".[[18]](#cite_note-18)[[19]](#cite_note-19) [[Image:Thalidomide-structures.png|thumb|right|The two enantiomers of thalidomide:  
Left: (*S*)-thalidomide  
Right: (*R*)-thalidomide]] Thalidomide is [racemic](/wiki/Racemic_mixture); the individual enantiomers can [racemize](/wiki/Racemization) due to the acidic hydrogen at the [chiral centre](/wiki/Chiral_centre), which is the carbon of the glutarimide ring bonded to the phthalimide substituent. The racemization process can occur [*in vivo*](/wiki/In_vivo)[[20]](#cite_note-20)[[21]](#cite_note-21)[[22]](#cite_note-22) so that any plan to administer a purified single enantiomer to avoid the teratogenic effects will most likely be in vain.[[21]](#cite_note-21)[[23]](#cite_note-23)[[24]](#cite_note-24)

### Cereblon[[edit](/index.php?title=(none)&action=edit&section=8)]

Several studies have now shown that the mechanism of action for thalidomide involves binding to the protein [cereblon](/wiki/Cereblon), a ubiquitin ligase substrate adapter protein,[[25]](#cite_note-25) Two months after Talimol went on sale, pharmaceutical companies sent physicians letters warning about the risk of birth defects.<ref name=pmid14076167/> It was not until March 2, 1962, that both drugs were banned from the Canadian market by the FDD, and soon afterward physicians were warned to destroy their supplies.<ref name=pmid14076167/>

### Leprosy treatment[[edit](/index.php?title=(none)&action=edit&section=10)]

In 1964, Israeli physician [Jacob Sheskin](/wiki/Jacob_Sheskin) administered thalidomide to a patient critically ill with leprosy. The patient exhibited [erythema nodosum leprosum (ENL)](/wiki/Erythema_nodosum), a painful skin condition, one of the complications of [leprosy](/wiki/Leprosy). This was attempted despite the ban on thalidomide's use, but results were favourable: the patient slept for hours and was able to get out of bed without aid upon awakening. A clinical trial studying the use of thalidomide in leprosy soon followed.[[36]](#cite_note-36) Thalidomide has been used by Brazilian physicians as the drug of choice for the treatment of severe ENL since 1965, and by 1996, at least 33 cases of thalidomide embryopathy were recorded in people born in Brazil after 1965.[[37]](#cite_note-37) Since 1994, the production, dispensing, and prescription of thalidomide have been strictly controlled, requiring women to use two forms of birth control and submit to regular pregnancy tests. Despite this, cases of thalidomide embryopathy continue,[[38]](#cite_note-38)[[39]](#cite_note-39) with at least 100 cases identified in Brazil between 2005 and 2010.[[40]](#cite_note-40) 5.8 million thalidomide pills were distributed throughout Brazil in this time period, largely to poor Brazilians in areas with poor access to healthcare, and these cases have occurred despite the controls.

In 1998 the FDA approved the drug's use in the treatment of ENL.[[41]](#cite_note-41) Because of thalidomide's potential for causing birth defects, the drug may be distributed only under tightly controlled conditions. The FDA required that [Celgene Corporation](/wiki/Celgene_Corporation), which planned to market thalidomide under the brand name *Thalomid*, establish a system for thalidomide education and prescribing safety (STEPS) oversight program. The conditions required under the program include limiting prescription and dispensing rights to authorized prescribers and pharmacies only, keeping a registry of all patients prescribed thalidomide, providing extensive patient education about the risks associated with the drug, and providing periodic pregnancy tests for women who take the drug.[[41]](#cite_note-41) In 2010, the [World Health Organisation (WHO)](/wiki/World_Health_Organisation) stated that it did not recommend thalidomide due the difficulty of adequately controlling its use, and due to the availability of [clofazimine](/wiki/Clofazimine).[[42]](#cite_note-42)

### Cancer treatment[[edit](/index.php?title=(none)&action=edit&section=11)]

Shortly after the teratogenic properties of thalidomide were recognized in the mid-1960s, its anti-cancer potential was explored and two clinical trials were conducted in people with advanced cancer, including some people with multiple myeloma; the trials were inconclusive.<ref name=Kyle>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

Little further work was done with thalidomide in cancer until the 1990s.<ref name=Kyle/>

[Judah Folkman](/wiki/Judah_Folkman) pioneered studies into the role of [angiogenesis](/wiki/Angiogenesis) (the proliferation and growth of blood vessels) in the development of cancer, and in the early 1970s had shown that [solid tumors](/wiki/Solid_tumors) could not expand without it.<ref name=NASbio>Patricia K Donahoe. [Judah Folkman: 1933–2008. A Biographical Memoir](http://www.nasonline.org/publications/biographical-memoirs/memoir-pdfs/folkman-judah.pdf) National Academy of Sciences, 2014</ref><ref name=Beilenberg>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> In 1993 he surprised the scientific world by hypothesizing the same was true of [blood cancers](/wiki/Blood_cancers),<ref name=Folkman>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> and the next year he published work showing that a [biomarker](/wiki/Biomarker) of angiogenesis was higher in all people with cancer, but especially high in people with blood cancers, and other evidence emerged as well.<ref name=Folkman/> Meanwhile, a member of his lab, Robert D'Amato, was looking for [angiogenesis inhibitors](/wiki/Angiogenesis_inhibitors), and discovered in 1994 that thalidomide inhibited angiogenesis.[[17]](#cite_note-17)[[43]](#cite_note-43) Around that time, the wife of a man who was dying of multiple myeloma and whom standard treatments had failed, called Folkman asking him about his anti-angiogenesis ideas.<ref name=Beilenberg/> Folkman convinced the patient's doctor to try thalidomide, and that doctor conducted a clinical trial of thalidomide for people with multiple myeloma in which about a third of the subjects responded to the treatment.<ref name=Beilenberg/> The results of that trial were published in the New England Journal of Medicine in 1999.[[44]](#cite_note-44) After further work was done by Celgene and others, in 2006 the U.S. Food and Drug Administration granted accelerated approval for thalidomide in combination with dexamethasone for the treatment of newly diagnosed [multiple myeloma](/wiki/Multiple_myeloma) patients.<ref name=Beilenberg/>[[45]](#cite_note-45)

## Thalidomide analogs[[edit](/index.php?title=(none)&action=edit&section=12)]

[Template:Main article](/wiki/Template:Main_article) The exploration of the [antiangiogenic](/wiki/Antiangiogenic) and immunomodulatory activities of thalidomide has led to the study and creation of thalidomide [analogs](/wiki/Analog_(chemistry)).[[46]](#cite_note-46)<ref name=pmid11740816>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> Celgene has sponsored numerous clinical trials with analogues to thalidomide, such as [lenalidomide](/wiki/Lenalidomide), that are substantially more powerful and have fewer side effects — except for greater [myelosuppression](/wiki/Myelosuppression).[[47]](#cite_note-47) In 2005, Celgene received FDA approval for [lenalidomide](/wiki/Lenalidomide) (Revlimid) as the first commercially useful derivative. Revlimid is available only in a restricted distribution setting to avoid its use during pregnancy. Further studies are being conducted to find safer compounds with useful qualities. Another more potent analog, [pomalidomide](/wiki/Pomalidomide), is now FDA approved.[[48]](#cite_note-48) Additionally, [apremilast](/wiki/Apremilast) was approved by the FDA in March 2014. These [thalidomide analogs](/wiki/Discovery_and_development_of_thalidomide_and_its_analogs) can be used to treat different diseases, or used in a regimen to fight two conditions.[[49]](#cite_note-49) Interest turned to [pomalidomide](/wiki/Pomalidomide), a [derivative](/wiki/Derivative_(chemistry)) of thalidomide marketed by [Celgene](/wiki/Celgene_Corporation). It is a very active anti-angiogenic agent <ref name=pmid11740816/> and also acts as an [immunomodulator](/wiki/Immunomodulator). Pomalidomide was approved in February 2013 by the U.S. [Food and Drug Administration](/wiki/Food_and_Drug_Administration) (FDA) as a treatment for relapsed and refractory [multiple myeloma](/wiki/Multiple_myeloma).<ref name=P1>[Template:Cite web](/wiki/Template:Cite_web)</ref> It received a similar approval from the [European Commission](/wiki/European_Commission) in August 2013, and is expected to be marketed in Europe under the brand name **Imnovid**.<ref name=P2>[Template:Cite web](/wiki/Template:Cite_web)</ref>

## Society and culture[[edit](/index.php?title=(none)&action=edit&section=13)]

### Regulatory approved uses[[edit](/index.php?title=(none)&action=edit&section=14)]

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Indications for thalidomide | | | | |
| **Labelled indication** | **USA (FDA)(date)<ref name = DM/><ref name = MSR/>** | **Australia (TGA) (date)<ref name = TGA/>** | **European Union (EMA) (date) <ref name = EMA>**[**Template:Cite web**](/wiki/Template:Cite_web)**</ref>** | **Literature support/Notes** |
| [Crohn's disease](/wiki/Crohn's_disease) | No [Template:Ref label](/wiki/Template:Ref_label) | No | No | Children and adolescents (in a small randomised clinical trial)[[50]](#cite_note-50) and adults (in open-label clinical trials).<ref name = Rev/> |
| [Erythema nodosum leprosum](/wiki/Erythema_nodosum_leprosum) (ENL) | Yes (1998) | Yes (2009) | No | Some literature support, including at least two randomised placebo-controlled trials.[[51]](#cite_note-51)[[52]](#cite_note-52)[[53]](#cite_note-53) |
| [Graft versus host disease](/wiki/Graft_versus_host_disease) (GVHD) | No [Template:Ref label](/wiki/Template:Ref_label) | No | No | Limited literature support.<ref name = Rev/> |
| Hematopoietic Stem Cell Transplantation | No [Template:Ref label](/wiki/Template:Ref_label) | No | No |  |
| HIV-associated wasting syndrome | No [Template:Ref label](/wiki/Template:Ref_label) | No | No |  |
| [Kaposi's sarcoma](/wiki/Kaposi's_sarcoma) (KS) | No [Template:Ref label](/wiki/Template:Ref_label) | No | No | Rare soft tissue cancer most commonly seen in the immunocompromised. Caused by the [Kaposi's sarcoma-associated herpesvirus](/wiki/Kaposi's_sarcoma-associated_herpesvirus) (KSHV). A phase II study has confirmed its efficacy.[[54]](#cite_note-54) |
| [Multiple myeloma](/wiki/Multiple_myeloma) | Yes (2006) | Yes (2009) | Yes (2008) | Numerous clinical trials have confirmed its efficacy, most often when used in combination with other medications.<ref name = Rev/> |
| Mycobacterial infection | No [Template:Ref label](/wiki/Template:Ref_label) | No | No | Mycobacterial infections include lepropsy, tuberculosis and mycobacterium avium complex (MAC) infections. |
| [Myelodysplastic syndrome](/wiki/Myelodysplastic_syndrome) | No [Template:Ref label](/wiki/Template:Ref_label) | No | No |  |
| Primary brain malignancy | No [Template:Ref label](/wiki/Template:Ref_label) | No | No |  |
| Recurrent [aphthous ulcers](/wiki/Aphthous_ulcers) | No [Template:Ref label](/wiki/Template:Ref_label) | No | No |  |

[Template:Note label](/wiki/Template:Note_label): designated [Orphan drug](/wiki/Orphan_drug) under the [Orphan Drug Act of 1983](/wiki/Orphan_Drug_Act_of_1983)

### Birth defects crisis[[edit](/index.php?title=(none)&action=edit&section=15)]

[thumb|Baby born to a mother who had taken thalidomide while pregnant](/wiki/Image:NCP14053.jpg) In the late 1950s and early 1960s, more than 10,000 children in 46 countries were born with [deformities](/wiki/Deformities) such as [phocomelia](/wiki/Phocomelia) as a consequence of thalidomide use.[[55]](#cite_note-55) The severity and location of the deformities depended on how many days into the pregnancy the mother was; thalidomide taken on the 20th day of pregnancy caused central brain damage, day 21 would damage the eyes, day 22 the ears and face, day 24 the arms, and leg damage would occur if taken up to day 28. Thalidomide did not damage the foetus if taken after 42 days gestation.[[33]](#cite_note-33) It is not known exactly how many worldwide victims of the drug there have been, although estimates range from 10,000 to 20,000[[26]](#cite_note-26) to 100,000.[[33]](#cite_note-33) Despite the side effects, thalidomide was sold in pharmacies in Canada until 1962;<ref name=pmid14076167/>[[56]](#cite_note-56)[thumb|right|These artificial limbs were made for an affected child in the 1960s by the](/wiki/File:Artificial_limbs_for_a_thalidomide_child,_1961-1965._(9660575567).jpg) [Department of Health and Social Security's](/wiki/Department_of_Health_and_Social_Security) Limb Fitting Centre in [Roehampton](/wiki/Roehampton), London In the United Kingdom, the drug was licensed in 1958 and withdrawn in 1961. Of the approximately 2,000 babies born with defects, around half died within a few months and 466 survived to at least 2010.[[57]](#cite_note-57) In Spain, thalidomide was widely available throughout the 1970s, perhaps even into the 1980s. There were two reasons for this. First, state controls and safeguarding were poor; indeed, it was not until 2008 that the government even admitted the country had ever imported thalidomide. Second, Grünenthal failed to insist that its sister company in Madrid warn Spanish doctors, and permitted it to not warn them. The Spanish advocacy group for victims of thalidomide estimates that in 2015, there were 250–300 living victims of thalidomide in Spain.[[58]](#cite_note-58) The Australian obstetrician [William McBride](/wiki/William_McBride_(doctor)) and the German [paediatrician](/wiki/Paediatrician) [Widukind Lenz](/wiki/Widukind_Lenz) suspected a link between birth defects and the drug, a theory Lenz proved in 1961.[[59]](#cite_note-59)[[60]](#cite_note-60) McBride was later awarded a number of honors, including a medal and prize money by L'Institut de la Vie in Paris.[[61]](#cite_note-61) Further animal tests were conducted by Dr George Somers, Chief Pharmacologist of [Distillers Company](/wiki/Distillers_Company) in Britain, which showed foetal abnormalities in rabbits.[[62]](#cite_note-62) Similar results were also published showing these effects in rats [[63]](#cite_note-63)[[64]](#cite_note-64) and other species.[[65]](#cite_note-65) In [East Germany](/wiki/East_Germany), the head of the central pharmacy control commission, Friedrich Jung, suspected an antivitaminic effect of thalidomide as derivative of [glutamic acid](/wiki/Glutamic_acid).[[66]](#cite_note-66) Meanwhile, in [West Germany](/wiki/West_Germany), it took some time before the increase in [dysmelia](/wiki/Dysmelia) at the end of the 1950s was connected with thalidomide. In 1958 Karl Beck, a former pediatric doctor in [Bayreuth](/wiki/Bayreuth) wrote an article in a local newspaper claiming a relationship between nuclear weapons testing and cases of dysmelia in children.<ref name=daeb/> Based on this, [FDP](/wiki/Free_Democratic_Party_(Germany)) [whip](/wiki/Whip_(politics)) [Erich Mende](/wiki/Erich_Mende) requested an official statement from the federal government.<ref name=daeb/> For statistical reasons, the main data series used to research dysmelia cases started by chance at the same time as the approval date for thalidomide.<ref name=daeb>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> After the Nazi regime with its [Law for the Prevention of Hereditarily Diseased Offspring](/wiki/Law_for_the_Prevention_of_Hereditarily_Diseased_Offspring) used mandatory statistical monitoring to commit various [crimes](/wiki/Action_T4), western Germany had been very reluctant to monitor [congenital disorders](/wiki/Congenital_disorder) in a similarly strict way.[[67]](#cite_note-67) The parliamentary report rejected any relation with radioactivity and the abnormal increase of dysmelia.<ref name=daeb/> Also the DFG research project installed after the Mende request was not helpful. The project was led by pathologist [Franz Büchner](/wiki/Franz_Büchner_(pathologist)) who ran the project to propagate his [teratological](/wiki/Teratology) theory. Büchner saw lack of healthy nutrition and behavior of the mothers as being more important than genetic reasons.[[67]](#cite_note-67) Furthermore, it took a while to install a Surgeon General in Germany; the [Federal Ministry of Health (Germany)](/wiki/Federal_Ministry_of_Health_(Germany)) was not founded until 1962, some months after thalidomide was banned from the market.<ref name=daeb/> In Germany approximately 2,500 thalidomide babies were born.[[60]](#cite_note-60) Several countries either restricted the drug's use or never approved it. Ingeborg Eichler, a member of the [Austrian](/wiki/Austria) pharmaceutical admission conference, enforced thalidomide (tradename Softenon) being sold under the rules of [prescription medication](/wiki/Prescription_medication) and as a result relatively few affected children were born in Austria and Switzerland.[[68]](#cite_note-68) In the United States, [pharmacologist](/wiki/Pharmacologist) [Frances Oldham Kelsey](/wiki/Frances_Oldham_Kelsey) [M.D.](/wiki/M.D.) withstood pressure from the [Richardson-Merrell](/wiki/Marion_Merrell_Dow) company and refused [Food and Drug Administration (FDA)](/wiki/Food_and_Drug_Administration_(United_States)) approval to market thalidomide, saying further studies were needed.[[55]](#cite_note-55) This reduced the impact of thalidomide in United States patients. Although thalidomide was never approved for sale in the United States at the time, millions of tablets had been distributed to physicians during a clinical testing program. It was impossible to know how many pregnant women had been given the drug to help alleviate morning sickness or as a sedative.[[69]](#cite_note-69)

### Aftermath of scandal[[edit](/index.php?title=(none)&action=edit&section=16)]

The numerous reports of malformations in babies brought about the awareness of the side effects of the drug on pregnant women. The birth defects caused by the drug thalidomide can range from moderate malformation to more severe forms. Possible birth defects include phocomelia, dysmelia, amelia, bone hypoplasticity, and other congenital defects affecting the ear, heart, or internal organs.<ref name=pmid15172781/> Franks et al. looked at how the drug affected newborn babies, the severity of their deformities, and reviewed the drug in its early years. Webb in 1963 also reviewed the history of the drug and the different forms of birth defects it had caused. "The most common form of birth defects from thalidomide is shortened limbs, with the arms being more frequently affected. This syndrome is the presence of deformities of the long bones of the limbs resulting in shortening and other abnormalities."<ref name=pmid14076167/>

#### Germany[[edit](/index.php?title=(none)&action=edit&section=17)]

In 1968, a large criminal trial began in Germany, charging several Grünenthal officials with negligent homicide and injury. After Grünenthal settled with the victims in April 1970, the trial ended in December 1970 with no finding of guilt. As part of the settlement, Grünenthal paid 100 million [DM](/wiki/Deutsche_Mark) into a special foundation; the German government added 320 million DM. The foundation paid victims a one-time sum of 2,500-25,000 DM (depending on severity of disability) and a monthly stipend of 100-450 DM. The monthly stipends have since been raised substantially and are now paid entirely by the government (as the foundation had run out of money). Grünenthal paid another 50 million Euros into the foundation in 2008.

On 31 August 2012, Grünenthal chief executive Harald F. Stock, PhD, who served as the Chief Executive Officer of Grünenthal GmbH from January 2009 to May 28, 2013 and was also a Member of Executive Board until May 28, 2013, apologized for the first time for producing the drug and remaining silent about the birth defects.[[70]](#cite_note-70) At a ceremony, Stock unveiled a statue of a disabled child to symbolize those harmed by thalidomide and apologized for not trying to reach out to victims for over 50 years. At the time of the apology, there were 5,000 to 6,000 sufferers still alive. Victim advocates called the apology "insulting" and "too little, too late", and criticized the company for not compensating victims. They also criticized the company for their claim that no one could have known the harm the drug caused, arguing that there were plenty of red flags at the time.[[71]](#cite_note-71)

#### United Kingdom[[edit](/index.php?title=(none)&action=edit&section=18)]

In 1968, after a long campaign by [*The Sunday Times*](/wiki/The_Sunday_Times), a compensation settlement for the UK victims was reached with [Distillers Company](/wiki/Distillers_Company) (now part of [Diageo](/wiki/Diageo)), which had distributed the drug in the UK.[[72]](#cite_note-72)[[73]](#cite_note-73) This compensation, which is distributed by the Thalidomide Trust in the UK, was substantially increased by Diageo in 2005.[[74]](#cite_note-74) The UK Government gave survivors a grant of £20 million, to be distributed through the Thalidomide Trust, in December 2009.[[75]](#cite_note-75)

#### Australia[[edit](/index.php?title=(none)&action=edit&section=19)]

Melbourne woman Lynette Rowe, who was born without limbs, is leading an Australian [class action](/wiki/Class_action) lawsuit against the drug's manufacturer, Grünenthal, which fought to have the case heard in Germany. The [Supreme Court of Victoria](/wiki/Supreme_Court_of_Victoria) dismissed Grünenthal's application in 2012, and the case was heard in Australia. More than a hundred Australian thalidomide survivors are involved in the class action, according to Rowe's lawyer.[[76]](#cite_note-76) On 17 July 2012, Lynette Rowe was awarded an out-of-court settlement, believed to be in the millions of dollars and paving the way for class action victims to receive further compensation. [[77]](#cite_note-77)

#### Canada[[edit](/index.php?title=(none)&action=edit&section=20)]

The drug thalidomide's birth defects in children affected many people's lives, and from these events came the formation of the group called The Thalidomide Victims Association of Canada, a group of 120 Canadian survivors.[[78]](#cite_note-78)[[79]](#cite_note-79) Their goal was to prevent future usage of drugs that could be of potential harm to mothers and babies. The members from the thalidomide victims association were involved in the STEPS program, which aimed to prevent teratogenicity.<ref name=pmid15172781/>

The effects of thalidomide increased fears regarding the safety of pharmaceutical drugs. The Society of Toxicology of Canada was formed after the effects of thalidomide were made public, focusing on toxicology as a discipline separate from pharmacology.<ref name=pmid12909394>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> The need for the testing and approval of the toxins in certain pharmaceutical drugs became more important after the disaster. The Society of Toxicology of Canada is responsible for the Conservation Environment Protection Act, focusing on researching the impact to human health of chemical substances.<ref name=pmid12909394/> Thalidomide brought on changes in the way drugs are tested, what type of drugs are used during pregnancy, and increased the awareness of potential side effects of drugs.

#### United States[[edit](/index.php?title=(none)&action=edit&section=21)]

[thumb|upright|1962: FDA pharmacologist](/wiki/Image:Frances_Oldham_Kelsey_and_John_F._Kennedy.jpg) [Frances Oldham Kelsey](/wiki/Frances_Oldham_Kelsey) receives the [President's Award for Distinguished Federal Civilian Service](/wiki/President's_Award_for_Distinguished_Federal_Civilian_Service) from President [John F. Kennedy](/wiki/John_F._Kennedy) for blocking sale of thalidomide in the United States. For correctly denying the application despite the pressure from Richardson-Merrell, Kelsey eventually received the President's Award for Distinguished Federal Civilian Service at a 1962 ceremony with President [John F. Kennedy](/wiki/John_F._Kennedy). In September 2010, the FDA honored Kelsey with the first Kelsey award. The award, given annually to an FDA staff member, came 50 years after Kelsey, then a new medical officer at the agency, first reviewed the application from the William S. Merrell Company of Cincinnati.[[80]](#cite_note-80) Cardiologist [Helen B. Taussig](/wiki/Helen_B._Taussig) learned of the damaging effects of the drug thalidomide on newborns and in 1967, testified before Congress on this matter after a trip to Germany where she worked with infants suffering from [phocomelia](/wiki/Phocomelia)(severe limb deformities). As a result of her efforts, thalidomide was banned in the United States and Europe.[Template:Citation needed](/wiki/Template:Citation_needed)

### Notable people affected[[edit](/index.php?title=(none)&action=edit&section=22)]

[thumb|right|Niko von Glasow, German filmmaker](/wiki/File:Niko_von_Glasow.jpg)

* [Mat Fraser](/wiki/Mat_Fraser), musician, actor and performance artist born with [phocomelia](/wiki/Phocomelia) of both arms[Template:Citation needed](/wiki/Template:Citation_needed)
* [Alvin Law](/wiki/Alvin_Law), radio broadcaster, born without arms[Template:Citation needed](/wiki/Template:Citation_needed)
* [Tony Meléndez](/wiki/Tony_Meléndez), award-winning singer and guitarist who plays with his feet and has been recognized by [Pope John Paul II](/wiki/Pope_John_Paul II) and [U.S. President](/wiki/U.S. President) [Ronald Reagan](/wiki/Ronald_Reagan)[Template:Citation needed](/wiki/Template:Citation_needed)
* [Thomas Quasthoff](/wiki/Thomas_Quasthoff), an internationally acclaimed bass-baritone, who describes himself: "1.34 meters tall, short arms, seven fingers — four right, three left — large, relatively well-formed head, brown eyes, distinctive lips; profession: singer"[[81]](#cite_note-81)\*[Niko von Glasow](/wiki/Niko_von_Glasow) produced a documentary called "[NoBody's Perfect](/wiki/NoBody's_Perfect)", based on the lives of 12 people affected by the drug, which was released in 2008[[82]](#cite_note-82)[[83]](#cite_note-83)\*[Terry Wiles](/wiki/Terry_Wiles), born with phocomelia of both arms and legs, has become known internationally through the television drama [*On Giant's Shoulders*](/wiki/On_Giant's_Shoulders) and the best-selling book of the same name[Template:Citation needed](/wiki/Template:Citation_needed)
* [Lorraine Mercer](/wiki/Lorraine_Mercer) [MBE](/wiki/Order_of_the_British_Empire) of the United Kingdom, born with phocomelia of both arms and legs, is the only thalidomide survivor to carry the Olympic Torch<ref name=Tamplin>[Template:Cite news](/wiki/Template:Cite_news)</ref>

### Change in drug regulations[[edit](/index.php?title=(none)&action=edit&section=23)]

The disaster prompted many countries to introduce tougher rules for the testing and licensing of drugs, such as the [Kefauver Harris Amendment](/wiki/Kefauver_Harris_Amendment)[[84]](#cite_note-84) (U.S.) and [Directive 65/65/EEC1](/wiki/Directive_65/65/EEC1) (E.U.).[[85]](#cite_note-85) In the United States, the new regulations strengthened the FDA, among other ways, by requiring applicants to prove efficacy and to disclose all side-effects encountered in testing.[[55]](#cite_note-55) The FDA subsequently initiated the [Drug Efficacy Study Implementation](/wiki/Drug_Efficacy_Study_Implementation) to reclassify drugs already on the market.

## Research[[edit](/index.php?title=(none)&action=edit&section=24)]

Investigational uses include:

* AIDS wasting syndrome,[[86]](#cite_note-86) associated diarrhoea[[87]](#cite_note-87) and [Kaposi's sarcoma](/wiki/Kaposi's_sarcoma).<ref name = Rev>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>
* [Renal cell carcinoma](/wiki/Renal_cell_carcinoma) (RCC)<ref name = Rev/>[[88]](#cite_note-88)\* [Glioblastoma multiforme](/wiki/Glioblastoma_multiforme)<ref name = Rev/>
* [Prostate cancer](/wiki/Prostate_cancer)<ref name = Rev/>
* [Melanoma](/wiki/Melanoma)<ref name = Rev/>
* [Colorectal cancer](/wiki/Colorectal_cancer)<ref name = Rev/>
* [Crohn's disease](/wiki/Crohn's_disease)<ref name = Rev/>
* [Rheumatoid arthritis](/wiki/Rheumatoid_arthritis)<ref name = Rev/>
* [Behcet's syndrome](/wiki/Behcet's_syndrome)[[89]](#cite_note-89)\* [Breast cancer](/wiki/Breast_cancer)<ref name = Rev/>
* [Head and neck cancer](/wiki/Head_and_neck_cancer)<ref name = Rev/>
* [Ovarian cancer](/wiki/Ovarian_cancer)<ref name = Rev/>
* Chronic heart failure<ref name = Rev/>
* Graft-versus-host disease<ref name = Rev/>

## See also[[edit](/index.php?title=(none)&action=edit&section=25)]

* [Immunomodulatory drug](/wiki/Immunomodulatory_drug)
* [Discovery and development of thalidomide and its analogs](/wiki/Discovery_and_development_of_thalidomide_and_its_analogs)
* [Drug of last resort](/wiki/Drug_of_last_resort)
* [Health crisis](/wiki/Health_crisis)
* [Holt-Oram syndrome](/wiki/Holt-Oram_syndrome)
* [:Category:People with phocomelia](/wiki/Category:People_with_phocomelia)
* [Diethylstilbestrol](/wiki/Diethylstilbestrol)

## References[[edit](/index.php?title=(none)&action=edit&section=26)]

[Template:Reflist](/wiki/Template:Reflist)

## Further reading[[edit](/index.php?title=(none)&action=edit&section=27)]

* [Template:Cite book](/wiki/Template:Cite_book)
* [Template:Cite book](/wiki/Template:Cite_book)

## External links[[edit](/index.php?title=(none)&action=edit&section=28)]

* [WHO Pharmaceuticals Newsletter No. 2, 2003 – See page 11, Feature Article](http://www.who.int/entity/medicines/publications/newsletter/en/news2003_2.pdf)
* [CBC Digital Archives – Thalidomide: Bitter Pills, Broken Promises](http://archives.cbc.ca/IDD-1-75-88/science_technology/thalidomide/)

[Template:Immunosuppressants](/wiki/Template:Immunosuppressants)

[Template:Authority control](/wiki/Template:Authority_control)

[Category:Congenital amputations](/wiki/Category:Congenital_amputations) [Category:German inventions](/wiki/Category:German_inventions) [Category:Glutarimides](/wiki/Category:Glutarimides) [Category:Health disasters](/wiki/Category:Health_disasters) [Category:Immunosuppressants](/wiki/Category:Immunosuppressants) [Category:Leprosy](/wiki/Category:Leprosy) [Category:Phthalimides](/wiki/Category:Phthalimides) [Category:Teratogens](/wiki/Category:Teratogens) [Category:Withdrawn drugs](/wiki/Category:Withdrawn_drugs) [Category:Chirality](/wiki/Category:Chirality) [Category:Medical controversies](/wiki/Category:Medical_controversies) [Category:Health disasters in the United Kingdom](/wiki/Category:Health_disasters_in_the_United_Kingdom) [Category:Drugs with unknown mechanisms of action](/wiki/Category:Drugs_with_unknown_mechanisms_of_action)