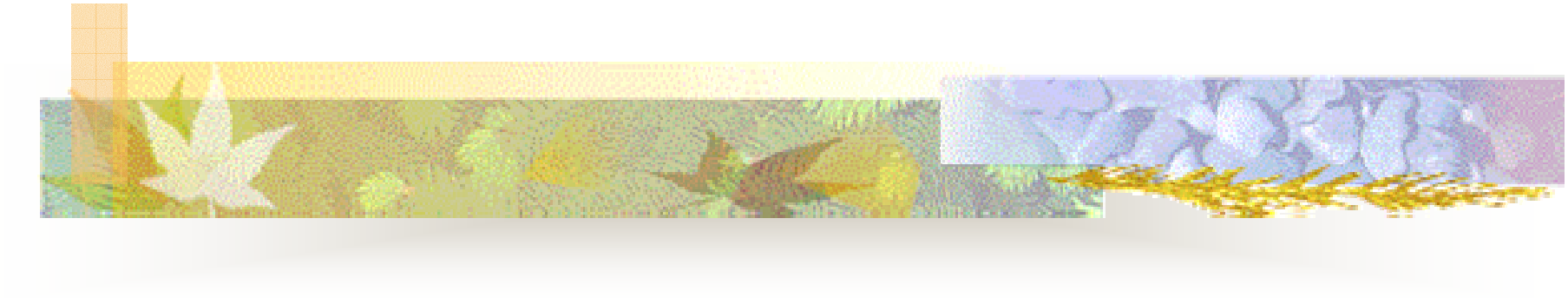
Thalidomide



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History of the drug

- Introduced by the pharmaceutical company, Grűnenthal in West Germany in 1953 under the brand name Contergan
- marketed from October 1, 1957 to 1961 as a sedative to treat insomnia and to reduce nausea (morning sickness) in pregnant women
- was available in around 50 countries under at least 40 names, but not in the U.S

History of the drug

- later found to be teratogenic in fetus when taken during the first 25-50 days of pregnancy

- absence of ears and deafness: 35th - 37th day
  absence of arms : 39th - 41st day
  phocomelia with 3 fingers: 43rd - 44th day
  thumbs with 3 joints: 46th - 48th day.

History of the drug : terms

- amelia : complete lack of a limb
- phocomelia :flipper-like hands and feet
- polymelia: presence of extra limbs

History of the drug

- Around 15,000 fetuses were damaged by thalidomide, of whom about 12,000 in 46 countries were born with birth defects, with only 8,000 of them surviving past the first year of life. Most of these survivors are still alive, nearly all with disabilities caused by the drug.

History of the drug

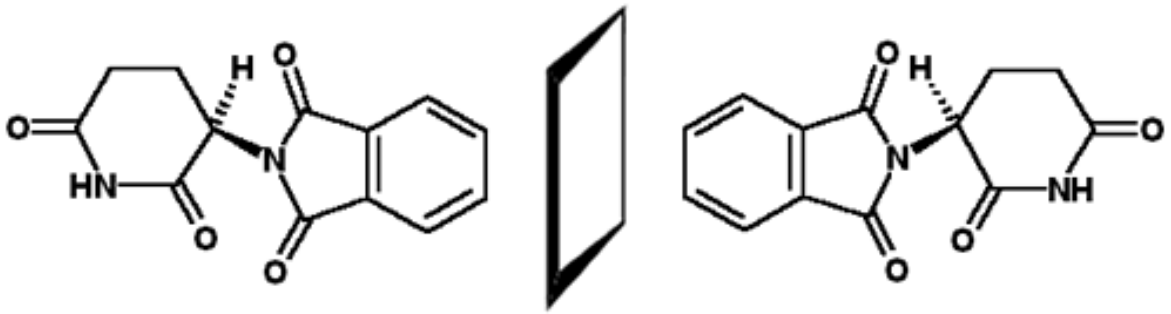
- Frances Oldham Kelsey

  ; a FDA reviewing medical officer in 1960, who insisted on safety data and the drug didn't get approved in the U.S

  → probably prevented thousands of deformities in the U.S

Mode of action

chemical structure : a racemate



R-Thalidomide
(sleep-inducing)

S-Thalidomide
(teratogenic)

Mode of action

- **Teratogenic mechanism : not clear**
- anti-angiogenic activity – inhibit the growth of blood vessels → decreased growth of the skeletal elements
- inhibition of mesenchymal (stem cells) proliferation in the limb bud

Clinical uses and MOA

- Mechanism of action : not clear
- erythema nodosum leprosum,
  a painful condition associated with leprosy
- MOA

: potent anti-inflammatory effects

Clinical uses and MOA

- **multiple myeloma**
- standard first line therapy in combination with dexametasone
- MOA

: inhibition of angiogenesis

(inhibition of the growth of new blood vessels that feed tumor cells)

Clinical uses and MOA

: inhibition of the growth and survival of stromal cells that help support and nourish the blood-producing cells

: altering production/activity of cytokines (chemical messengers)

Clinical uses and MOA

: altering the expression of adhesion molecules located on the surface if tumor cells and bone marrow stromal cells

: stimulation of T-cells – allow the patients' own immune system to attack cancer cells

Other clinical uses

- HIV-related symptoms, prostate cancer, lymphoma, Crohn's disease, Kaposi's sarcoma, etc

STEPS(System for Thalidomide Education & Prescribing Safety) program.

- female patients - prescriptions are not be given without a negative pregnancy test within 24 hours of treatment start; must take pregnancy tests regularly for a prescribed period, and must use two reliable forms of contraception while under treatment.
- male patients - use condoms because it is unknown whether thalidomide in sperm or semen affects fetal development.

Other side effects

- Fatigue, constipation, peripheral neuropathy, deep vein thrombosis, etc

Sales and Cost

- $308.6 million sales for Thalidomid in 2004
- $21 – $38 per 50 mg capsule in 2005

Name and other names

- 2-(2,6-Dioxo-3-piperidinyl)-1*H*-isoindole-1,3(2*H*)-dione
- Thalomid
- Actimid
- CC 4047
- IMiD 3
- Kevadon

CAS Registry

- **50-35-1**

- ** Reference
- 1.http://pubs.acs.org/cen/coverstory/83/8325thalidomide.html
- 2. http://www.celgene.com
- 3. http://enwikipedia.org/wiki/Thalidomide