Thalidomide

What does this medicine treat?

Thalidomide is a sedative drug introduced in the late 1950s that was used to treat morning sickness. [2] It was sold from 1957 until 1961, when it was withdrawn after being found to be a cause of birth defects.[3]

Thalidomide is now used to treat multiple myeloma (cancer of the plasma cells in bone marrow) it can also be combined with other drugs to treat and prevent skin symptoms of erythema nodosum leprosum (also known as leprosy). It is in a class of medications called immunomodulatory agents. These drugs are used to strengthen the immune system and to block natural substances that cause swelling.

How this medicine is used

Thalidomide is manufactured in a capsule that is taken by mouth, with water once a day, according to Celgene Corporation, the company now making Thalidomide. This capsule should be taken at bedtime and at least one hour after the evening meal. It may be prescribed multiple times per day, depending on the strength and reason for treatment. Thalidomide should be taken at the same time every day, regardless of how many times per day it is prescribed. It is imperative that Thalidomide be taken exactly as prescribed.

Capsules are dispensed in individual packaging. This packaging should not be opened until ready for use. Should the capsule break and skin comes into contact with powder, wash hands and exposed area with soap and water.

Treatment length depends on how well symptoms respond to the treatment and if symptoms return once the drug is no longer taken. It is not unusual for treatment to be interrupted to adjust levels due to side effects. This should only be done under a doctor’s care.

Other uses for Thalidomide

Thalidomide has been successfully used to treat certain skin conditions involving swelling and irritation. It has also been used to treat complications associated with HIV such as ulcers in the mouth, HIV-associated diarrhea, HIV-related wasting syndrome, certain infections and Kaposi’s sarcoma (skin cancer). Thalidomide has also been shown to be a beneficial treatment for some types of cancer and tumors, severe weight loss in weakened immune system patients, and for complications after the bone marrow transplant in which the newly transplanted material attacks the recipient’s body, and Crohn’s disease.
**Warnings**

If thalidomide is taken during pregnancy, it can cause severe birth defects or death to an unborn baby. Thalidomide should never be used by women who are pregnant or who could become pregnant while taking the drug. Even a single dose [1 capsule (regardless of strength)] taken by a pregnant woman during her pregnancy can cause severe birth defects.

Because of this toxicity and in an effort to make the chance of fetal exposure to THALOMID® (thalidomide) as negligible as possible, THALOMID® (thalidomide) is approved for marketing only under a special restricted distribution program approved by the Food and Drug Administration. This program is called the "SYSTEM FOR THALIDOMIDE EDUCATION AND PRESCRIBING SAFETY (S.T.E.P.S.*)". Under this restricted distribution program, only prescribers and pharmacists registered with the program are allowed to prescribe and dispense the product. In addition, patients must be advised of, agree to, and comply with the requirements of the S.T.E.P.S.* program in order to receive product.

**Thalidomide as a teratogen**

The original formulation of Bendectin contained Bentyl (dicylcomine hydrocloride) an antispasmodic used to control the nausea and vomiting of nervous stomach; Decapryn (doxylamine succinate) an antihistamine that had been used to alleviate nausea following radiation therapy in cancer patients; and pyridoxine (vitamin B-6) which was thought by some physicians to have a beneficial effect on the nausea of pregnancy.

In 1953 the regulations for marketing a new drug were not as restrictive as they are today. Since both Decapryn and Bentyl were Merrell products that had prior approval for marketing, the individual animal safety studies from these separate ingredients were accepted as proof of Bendectin's relative safety. Additional testing in animals was not required for the three-part combination and no specific studies were made of the drug's effects on the offspring of test animals.

Although Bendectin was designed for use specifically in pregnancy, only one clinical study was undertaken prior to marketing. In this study some 277 patients were given samples of Bendectin to evaluate the drug's ability to reduce symptoms of nausea and vomiting. In addition to pregnant women with morning sickness, the study population also included several children and women with motion sickness. There was no follow-up of the pregnant patients to determine any possible adverse effects to their babies.

Merrell filed a new drug application for Bendectin in June 1956. This NDA was approved by the Food and Drug Administration in just 28 days. In January 1959, the Merrell Company obtained the exclusive rights to market another drug. Thalidomide had been developed by a West German pharmaceutical company, Grunenthal. It was rapidly gaining popularity all over Europe as a "safe" sedative. Thalidomide was also included in some 50 over-the-counter products used for everything from colds and flu to the morning sickness of pregnancy.
Four months after obtaining the license for Thalidomide from its German manufacturer, Richardson Merrell began testing the drug by distributing 2,528,412 thalidomide tablets to 1,267 private physicians who gave them to 20,000 patients. At the same time these human studies were underway, the company also began animal testing. Although one of the indications for thalidomide was nausea and vomiting of pregnancy, no specific tests were done to look for possible adverse effects to the developing fetus.

Although Thalidomide was never approved for sale in the United States, millions of tablets had been distributed to physicians during the 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.

**Birth Defects**

As the horror of the Thalidomide tragedy made headlines around the world, the Food and Drug Administration started making an investigation of its files of adverse reaction reports searching for Thalidomide-related deformities.

It was this investigation that was to lead to the first questions about Bendectin's safety. In a letter dated December 17, 1962, the Director of the FDA's Bureau of Field Administration, A.E. Rayfield wrote to Frederic Lamb, General Counsel for the Wm. S. Merrell Company. His letter affirmed that the Thalidomide investigation had turned up four reports to the Food and Drug Administration of infants with birth defects whose mothers had taken Bendectin during pregnancy.

These reports included:
Infant born 1/15/61 Missing left thumb and right thumb. Club foot and heart disorders.
Infant born 12/22/60. Absence of left arm, some metatarsus varus of the left leg, left side of face flattened, both hands missing index fingers, bilateral club foot.
Infant born 5/10/62 Nasal bone with no airway. Fibulas missing from both legs, no knee caps or ankle bones, red mark on forehead between eyes.
Infant died 4/10/62 Atresia of extremities, imperforate anus.

Reports of Bendectin associated birth defects were coming in from other parts of the world as well. In an interoffice memo dated September 17, 1963, a Dr. Gerald Morson of Merrell wrote to his associate in Australia regarding two reports of malformations: "... in cases like this, it is hardly possible to be sure one way or the other whether any drug given during the pregnancy was directly or indirectly involved."

In a 1962 report in the American Journal of Obstetrics and Gynecology, Dr. P.M. Dunn reported the cases of four infants who were born with phocomelic limb malformations. In two cases, the mothers had taken thalidomide, but in the third case of twins with phocomelia the mother had taken Debendox, the British name for Bendectin. Dr. Dunn speculated, "... Thalidomide is only one of many new sedative and antiemetic drugs. It may well be that more than one has this teratogenic action."
Examples of Thalidomide birth defects

A 1962 photo of a baby born to a mother who had taken thalidomide while pregnant. The baby has an extra appendage connected to the foot and a malformation of the right arm.

Awards and Law Suits

U.S. Pharmacologist, M.D. Frances Oldham Kelsey, refused the FDA an application from the Merrill Corp. to market Thalidomide. She stated that further studies were needed, this reduced the impact of Thalidomide in U.S. patients. Although Thalidomide was never approved for sale in the U.S., millions of tablets had been distributed by physicians during clinical trials. It would be impossible to know how many pregnant women had taken Thalidomide for morning sickness or as a sedative.
M.D. Frances Oldham Kelsey was awarded the Presidents Award for Distinguished Federal Civilian Service by President Kennedy in 1962. Her refusal to grant the FDA approval, despite pressure from the Merrell Corp.

Notable People Affected by Thalidomide

- Rock Brenner, son of Yule Brenner, author of *Dark Remedy*
- Niko von Glasow, produced a documentary based on the lives of 12 people affected by the drug, which was released in 2008 entitled *Nobody's Perfect*
- Tony Melendez, award winning singer and guitarist who has become known internationally due to the recognition received from Pope John Paul II and U.S. President Ronald Reagan
- Terry Wiles, born with phocomelia of both arms and legs and has become known internationally through the television drama *On Giant's Shoulders* and the best-selling book of the same name
- Thomas Quasthoff, 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.

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