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Teratology Society Public Affairs Committee Position Paper: Thalidomide

PUBLIC AFFAIRS COMMITTEE†

Thalidomide was initially marketed as a sedative in Germany in 1957. The drug was withdrawn from the market in 1961 because prenatal exposure to the drug was shown to cause a specific pattern of malformation that included defects of the arms and legs; abnormalities of the eyes; and malformations of the heart, kidneys, and intestinal tract. Fortunately for those in the United States, the drug never received approval for marketing by the Food and Drug Administration (FDA) because of concern about the risk of peripheral neuritis in treated patients. However, based on recent clinical trials documenting 70–80% efficacy, thalidomide (Thalomid™) has now been approved as a treatment for erythema nodosum leprosum, a serious inflammatory condition in patients with Hansen's disease, also known as leprosy. At the same time, the FDA has imposed unprecedented restrictions on the drug's distribution, making it among the most tightly restricted drugs ever to be marketed in the United States.

Concern exists within the Teratology Society that such FDA approval may open the door for the use of thalidomide as a treatment for a number of off-label indications such as aphthous ulcers in patients with and without human immunodeficiency virus (HIV) infection, Behçet's disease, chronic graft-versus-host disease (GVHD), rash due to systemic lupus erythematosus (SLE), and other inflammatory dermatoses, refractory rheumatoid arthritis, uremic pruritus, severe atopic erythroderma, acquired immune deficiency syndrome (AIDS) wasting syndrome, microsporidioses diarrhea, macular degeneration, and Kaposi's sarcoma. These concerns and the issues concerning the release of thalidomide were recently summarized by Friedman and Kimmel ('99). For similar reasons, new reports of thalidomide teratogenesis are being heard from South America (Castilla et al., '96), and dermatologists in Mexico have already used thalidomide to treat more than 30 infants and children with severe atopic erythroderma, as well as treating more than 100 adults with other skin disorders, like actinic prurigo, polyarteritis nodosa, Behçet's disease, and lupus (Bates, '97). It seems likely that dermatologists in the United States will soon follow suit and begin using thalidomide for other serious dermatoses, now that it has become more available. For this reason, tight restrictions on the use of thalidomide are warranted.

In an attempt to minimize the number of women exposed to this drug during pregnancy, the Celgene Corporation has developed a program referred to as the System for Thalidomide Education and Prescribing Safety (STEPS). Thalidomide can only be prescribed in the United States by physicians who are registered in the STEPS program, and both male and female patients must comply with mandatory contraceptive measures, patient registration, and patient surveys. This is a three-step program that must be followed with all patients who are potential candidates for the drug: (1) patients must receive education regarding the potential benefits and side effects of thalidomide; (2) contraceptive counseling must be provided, including emergency contraception measures, and women of childbearing potential must be given pregnancy tests; and (3) patients must complete an informed consent form and participate in an ongoing mandatory and confidential survey. Prescribers who fail to comply with all three components of the program will not have their prescriptions honored at registered pharmacies. Furthermore, no more than a 4-week supply of the drug can be prescribed at any one time, with no automatic refills; in fact, during the first 4 weeks of treatment, it is recommended that females receive only a 1-week supply until the results of weekly pregnancy tests become available. Women must also use two reliable forms of contraception while taking the drug.

It is logical to expect that these safeguards will decrease the number of pregnant women who receive thalidomide. However, to suggest that such measures will be 100% effective may not be realistic. One need only look at the experience over the last 10 years with Accutane. Since 1989, when similar restrictions on its use were initiated, a number of women have inadvertently taken Accutane during early pregnancy. To the credit of the FDA and Celgene, it appears initially as though more effective safeguards have been established for thalidomide, but much work remains to be done.

†This position paper has been approved by the following members of the Public Affairs Committee of the Teratology Society: Jane Adams, Harpal S. Buttar, Christina Chambers, Tom F.X. Collins, John M. Graham, Jr., Kenneth Lyons Jones,* Sandra Kweder, Joe Mitala, Janine E. Polifka, and Bernard A. Schwetz.

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Given the fact that pregnant women may still be inadvertently exposed to thalidomide, the Teratology Society makes the following recommendations:

1. In whichever countries the drug is approved for use, federal agencies such as the FDA should monitor the proposed pregnancy use restrictions to ensure their effectiveness before any pregnant women are inadvertently treated with thalidomide. Currently, the STEPS database is being managed by independent investigators at the Slone Epidemiology Unit at Boston University, where information on fertile women will be collected at least monthly, and information on other patients will be collected every 3 months during thalidomide treatment.
2. In whichever countries the drug is approved for use, federal agencies such as the FDA should establish a method to monitor pregnancy outcome in women who do become pregnant while taking thalidomide.
3. Further research is encouraged to develop safer alternative drugs that are at least equally effective for conditions that thalidomide is used to treat.
4. A fund should be established to compensate children born since July 1998 with thalidomide embryopathy and their families.

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