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The Return of Thalidomide

Can Birth Defects Be Prevented?

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Abstract

Thalidomide, the drug that caused a worldwide epidemic of serious birth defects in the late 1950s and early 1960s, was recently approved by the US Food and Drug Administration (FDA) for use in treating the skin disease erythema nodosum leprosum, a complication of leprosy. The drug has also shown promise in the treatment of other serious diseases. If thalidomide is eventually approved for use in the US and other countries for treatment of diseases more prevalent than erythema nodosum leprosum, or if use of the drug for non-approved indications becomes widespread, hundreds of thousands of women with childbearing ability could be treated. If this should happen, can we prevent another epidemic of birth defects?

In an effort to prevent fetal exposures to thalidomide, the FDA mandated a comprehensive programme to regulate prescription, dispensing and use of the drug. The programme is designed to require registration of all participating prescribers, pharmacies and patients. It also requires use of effective methods of contraception and periodic pregnancy testing of all patients with childbearing ability during treatment. Prescribers are directed to counsel both female and male patients on the risks, benefits and proper use of the drug, as well as on the proper use of contraceptives during treatment. The patient is required to sign an informed consent form before beginning treatment. Prescription and dispensing of thalidomide will be tightly controlled. A thalidomide registry will monitor prescription, dispensing and use of the drug, and will investigate all reported fetal exposures.

This mandatory, but untested, programme promises to be effective at preventing fetal exposures to thalidomide, provided that patients, prescribers and pharmacists comply with all of its provisions. However, even if the programme proves to be successful in the US, there is concern that thalidomide may eventually be widely used in countries that may not require such stringent controls. In Brazil, where thalidomide is commercially available for treatment of leprosy patients, 33 cases of thalidomide embryopathy have already been reported in the literature. Even in countries that may tightly regulate the distribution and use of thalidomide, some patients may obtain the drug through black market sources. Should these events occur, many cases of thalidomide-induced birth defects could appear. Therefore, there is a need to develop nonteratogenic analogues of thalidomide that can provide effective treatment for erythema nodosum leprosum and other

serious conditions without increasing the potential for another epidemic of thalidomide-related birth defects.

On July 16 1998, the US Food and Drug Administration (FDA) approved the use of thalidomide for treatment of the skin disease erythema nodosum leprosum, a complication of leprosy (Hansen's disease). The drug is indicated for the acute treatment of moderate to severe erythema nodosum leprosum and as maintenance therapy for prevention and suppression of recurrence of erythema nodosum leprosum. Thalidomide is being marketed under the brand name of Thalomid® by Celgene Corporation of Warren, NJ, USA.

Thalidomide was first distributed in Europe and Canada in the late 1950s for use as a tranquilliser and for treatment of morning sickness in pregnant women. Thalidomide was promoted by its manufacturer as being 'nontoxic and safe for use by pregnant women'. This proved not to be the case. In 1961, physicians in Germany, the UK and Australia noted a sharp increase in the incidence of hypoplastic and aplastic malformations of the limbs.[1-3] That same year, Lenz in Germany[4] and McBride in Australia[2] suggested that these severe limb defects might be caused by thalidomide ingestion during pregnancy. The drug was also reported to cause peripheral neuritis, a painful and sometimes permanent numbing of the hands and feet, in some users.[5,6] By 1962, the drug had been removed from the market in most countries, and the incidence of hypoplastic and aplastic limb malformations dropped sharply.[7] However, by the time thalidomide had been withdrawn from the market, the drug had caused more than 10 000 cases of birth defects worldwide.[8]

In the US, only 17 infants with malformations were identified because the FDA never approved the drug for prescription use because of concerns over reports of peripheral neuritis associated with use of the drug.[9] Of the 17 cases, 10 resulted from investigative use of thalidomide in the US by more than 1200 physicians before the teratogenic effects of the drug were widely publicised, and 7 resulted from exposure to thalidomide obtained from sources outside the US.

Thalidomide appears to cause birth defects only during a 3-week period early in pregnancy. The critical period of exposure extends from day 21 through to day 40 of gestation.[10] Although it is not known precisely what the incidence of defects was when thalidomide was taken by the mother during the first trimester, almost 100% of pregnant women exposed during the critical period gave birth to babies with birth defects.[8,11]

After thalidomide was removed from the market, it was found to have immunosuppressive and anti-inflammatory properties, and it was found to be effective in the treatment of erythema nodosum leprosum in leprosy patients.[12] Thalidomide has also been used as an investigational drug to treat other immune-system-modulated diseases, including systemic lupus erythematosus, rheumatoid arthritis, Behçet's disease, graft-versus-host disease, aphthous ulcers and severe bodyweight loss in individuals with AIDS.[8,13] In addition to its immunosuppressive properties, thalidomide has been found to inhibit angiogenesis and could be useful in the treatment of neoplasms, diabetic retinopathy and macular degeneration.[14] Thalidomide has been tested in the treatment of a number of other disorders, and more uses for the drug are likely to be discovered in the future.

Can another epidemic of birth defects be prevented now that thalidomide has been approved for prescription use in the US and is likely to be approved in other countries? This article discusses the steps that the FDA and the drug manufacturer have taken to prevent thalidomide-affected pregnancies and considers the likelihood that such steps will be effective in preventing another epidemic of birth defects if the drug becomes widely used for disorders other than erythema nodosum leprosum.

1. Drugs on the Market that are Known Human Teratogens

Several drugs besides thalidomide are considered to be human teratogens but are available on the market for treatment of serious diseases. These drugs include androgenic hormones, cyclophosphamide, diethylstilbestrol, etretinate, isotretinoin, lithium, methotrexate (methylaminopterin), penicillamine, phenytoin (diphenylhydantoin), trimethadione and valproic acid (sodium valproate).[10,15] With the exception of isotretinoin, no restrictions are placed on the use of these drugs other than a warning that the drugs should not be used during pregnancy unless medically necessary. Many cases of human birth defects resulting from exposure to these teratogens have been reported in the literature. However, most infants with birth defects caused by exposure to these human teratogens are probably never reported in the literature, and the true incidence of these malformations is therefore unknown.

2. Experience with Isotretinoin

After a number of infants with birth defects were reported following use of the drug isotretinoin (Accutane®) by women for treatment of severe recalcitrant cystic acne, an FDA advisory committee considered removing the drug from the market in the US. However, because of its unique efficacy in treating severe acne, the manufacturer, Roche Pharmaceuticals, proposed an alternative to removing the drug from the market or restricting its use.[16,17] The manufacturer suggested a programme designed to reduce the risk of pregnancy among women taking the drug. The advisory committee recommended this programme to the FDA, and in 1988, the Roche Pregnancy Prevention Program for Women on Accutane began. The drug is presently available by prescription in the US and 93 other countries. Labels in other countries contain warnings about the risk of fetal exposure and use selected parts of the Pregnancy Prevention Program (Roche, personal communication).

The Roche Pregnancy Prevention Program is a voluntary programme targeted at both prescribers and patients, and programme materials are distributed to dermatologists and other identified prescribers of isotretinoin. The materials include a patient-qualification checklist, an informational brochure for patients, information about contraceptives, referral forms for a visit to another physician for contraceptive counselling, and an informed consent form. The drug is available in a 10-capsule blister pack that includes warnings about the risks of becoming pregnant while taking isotretinoin. A symbol behind each capsule is intended to convey the meaning 'avoid pregnancy,' and a line drawing of malformations associated with isotretinoin use is included.[18] Although this voluntary Pregnancy Prevention Program is a major improvement over just putting warnings in package inserts for prescription drugs that are human teratogens, the programme has not been entirely successful in preventing birth defects associated with the drug.

Results from a survey taken in the US for the 5-year period between 1989 and 1993 show that 402 pregnancies occurred among 124 216 women treated with isotretinoin (3.4 pregnancies per 1000 courses of treatment).[18] Most of these pregnancies were electively terminated, but 8 of the 32 liveborn infants had birth defects. In the same study period, 136 pregnancies occurred during the month after users discontinued treatment (13.4 pregnancies per 1000 courses of treatment). The Pregnancy Prevention Program tries to discourage pregnancy immediately following treatment with isotretinoin. Some women failed to comply with the provisions of the programme. Although nearly all of the women enrolled in the programme understood the teratogenic risks of isotretinoin use and of the need to avoid pregnancy, some women took the drug before obtaining a negative pregnancy test or before menses had begun. Others failed to use effective means of birth control preceding, during or immediately after treatment.

In the UK, 76 pregnancies were reported to have been electively terminated during the 5-year period from 1992 to 1996 because of fetal exposure to

isotretinoin.[19] The authors of that report indicated that the actual number of pregnancy terminations was probably much higher because of significant under-reporting of elective abortions following isotretinoin exposure during pregnancy. In South Australia, 18 terminated pregnancies were reported following fetal exposure to isotretinoin during the 9-year period between 1985 and 1993 (3.1 terminations per 1000 courses of treatment).[20] Pregnancies occurring during isotretinoin treatment have also been reported in Canada.[21]

Although the Roche Pregnancy Prevention Program may reduce the risk for pregnancy during isotretinoin treatment by more than 10-fold,[18] many exposures to isotretinoin continue to occur during pregnancy. This voluntary programme has had limited success in preventing pregnancy during isotretinoin treatment. Incomplete compliance with the provisions of the programme has resulted in a number of elective abortions of exposed fetuses and in the birth of infants with isotretinoin-induced malformations.

3. System for Thalidomide Education and Prescribing Safety (STEPS) Programme for Thalidomide Use

The voluntary Pregnancy Prevention Program described in section 2 does not prevent all fetal exposures to isotretinoin. A similar voluntary pregnancy prevention programme for thalidomide use could lead to an unacceptable number of exposed pregnancies and severely affected fetuses. To minimise the risk for fetal exposure to thalidomide, the drug manufacturer developed a mandatory programme to regulate prescription, dispensing and use of the drug. This programme is called the System for Thalidomide Education and Prescribing Safety (STEPS) programme.[22] With FDA approval of this programme, thalidomide became the most extensively regulated prescription drug in US history. The STEPS programme requires registration by prescribers, pharmacies and patients before thalidomide can be prescribed and dispensed. Prescription, dispensing and use of the drug is being monitored by the Slone Epidemiology Unit at the Boston University School of Public Health and by the FDA. All fetal exposures reported during treatment will be investigated by Celgene and the FDA. The FDA indicates it will evaluate data collected by the STEPS programme and will make changes to the programme, if necessary, to ensure its effectiveness and prevent fetal exposures to the drug (FDA, personal communication).

The basic provisions of the STEPS programme are summarised below.

3.1 Requirements for Prescribers and Patients

Prescribers considering treating patients with thalidomide are to contact Celgene to request a STEPS folder. The folder contains all of the materials necessary for a prescriber to participate in the STEPS programme and to enrol a patient in the programme. Prescribers must register with the STEPS Prescriber Registry by completing a Prescriber Registration Card and by agreeing to prescribe thalidomide in accordance with the terms of the STEPS programme. Prescribers are required to wait for confirmation of registration prior to prescribing thalidomide.

3.1.1 Prescribing Thalidomide for Female Patients

During the initial patient visit, the prescriber is asked to determine the appropriateness of thalidomide therapy versus therapeutic alternatives. The programme requires patients to be counselled on the risk for birth defects, peripheral neuropathy and other adverse effects, and on precautions to be taken during thalidomide therapy. A brochure containing essential information for women taking thalidomide is provided in the STEPS folder for use during patient counselling. An optional videotape containing this material is available from Celgene at the prescriber's request.

During the initial patient visit, the prescriber is also asked to determine if the patient has childbearing potential. If the patient has had a hysterectomy, has been postmenopausal for at least 24 months, or has had no menses for at least 24 consecutive months, the patient does not have to be advised about the use of contraceptives during treatment.

However, if the patient is sexually mature and physically capable of bearing a child, then she is to be given contraceptive counselling, including counselling on emergency contraception. Prescribers may provide the contraceptive counselling themselves, or they may use the Patient Referral Form provided in the STEPS folder to refer patients to another healthcare professional for contraceptive counselling. Patients with childbearing potential are to be advised to use 2 effective forms of contraception at the same time, starting at least 4 weeks before beginning therapy with thalidomide and continuing throughout the therapy and for at least 4 weeks after stopping therapy. Informational brochures on contraceptive choices and emergency contraception are also provided in the STEPS folder for use by the prescriber or other healthcare professionals in counselling female patients.

Once the prescriber decides to start a patient on thalidomide therapy, the prescriber is directed to repeat the patient counselling on the risks and benefits of thalidomide therapy. For women with childbearing potential, the prescriber is to repeat the counselling on the use of contraceptives and emergency contraceptives. The prescriber is directed to ask all female patients 5 specific 'yes-no' questions to assess their understanding of the requirements for taking the drug. If the patient fails to answer all questions correctly, the prescriber should review the material the patient does not understand and readminister the quiz until the patient answers all questions correctly. If the prescriber does not believe that the patient is capable of understanding the requirements for taking thalidomide, the prescriber is requested to reconsider the appropriateness of thalidomide therapy.

Before starting thalidomide therapy, the prescriber is directed to perform a pregnancy test on patients with childbearing potential. The pregnancy test is to be given within 24 hours of the start of therapy, and negative results are to be reported in written form. Women with childbearing potential are also to be given a pregnancy test every week for the first 4 weeks of treatment, then every 4 weeks thereafter if their menstrual cycles are regular. If their menstrual cycles are irregular, the patients should be given a pregnancy test every 2 weeks thereafter. If a patient misses her period or if there is any abnormal menstrual bleeding, the patient should be counselled and given a pregnancy test. If pregnancy does occur during treatment, the drug should be discontinued immediately. Any suspected fetal exposure to thalidomide is required to be reported immediately to the FDA and to Celgene. The patient should be referred immediately to an obstetrician/gynaecologist experienced in reproductive toxicity for further evaluation and counselling.

Before beginning thalidomide therapy, the prescriber is required to have the patient complete and sign an informed consent form. The consent form should be read to the patient, and parent or legal guardian if appropriate, in the language of their choice and must be signed by the prescriber and the patient (and the parent or legal guardian if appropriate). The prescriber is to keep a copy with the patient record, mail a copy to the Slone Epidemiology Unit, and instruct the patient to keep a copy and give a further copy to the pharmacist along with the prescription. Before writing a prescription for thalidomide for the patient, the prescriber is required to have the patient complete a confidential patient survey enrolment form which the prescriber then mails to the Slone Epidemiology Unit.

Once all of the above requirements of the STEPS programme have been completed, the prescriber may write a prescription for the patient. Prescriptions cannot be issued by telephone. No more than a 4-week supply of thalidomide can be prescribed, with no automatic refills. All prescriptions should be filled within 7 days. It is recommended that female patients of childbearing potential receive no more than a 1-week supply for each of the first 4 weeks of therapy to coincide with weekly pregnancy testing requirements.

During the first 4 weeks of therapy, the patient should return to the prescriber for follow-up examinations every week. During the visit, the prescriber is directed to repeat patient counselling and perform a pregnancy test on the patient. The preg-

nancy test is required to be performed not more than 24 hours before the prescriber provides a subsequent prescription. Pregnancy tests are expected to be performed even if continuous abstinence is the chosen method of birth control. If the test is negative, the prescriber can provide a prescription for a 1-week supply of thalidomide.

After the first 4-week period of treatment, the prescriber is asked to repeat patient counselling and perform a pregnancy test every 4 weeks if the patient's menstrual cycles are regular, or every 2 weeks if the cycles are irregular. If the pregnancy test is negative, the prescriber can provide a prescription for no more than a 4-week supply of thalidomide for therapy. Every month during treatment, the prescriber is required to have the patient complete a follow-up survey form which the prescriber then mails to the Slone Epidemiology Unit.

3.1.2 Prescribing Thalidomide for Male Patients

During the initial visit by a male patient, the prescriber should determine the appropriateness of thalidomide therapy versus therapeutic alternatives. The patient is to be counselled on the risk for birth defects, peripheral neuropathy and other adverse effects, along with the precautions associated with thalidomide therapy. An informational brochure containing essential information for men taking thalidomide is provided in the STEPS folder. Because it is not known if thalidomide is present in the semen or sperm of men ingesting the drug, the prescriber should counsel male patients to use a latex condom every time they have sexual intercourse with a woman, even if they have undergone a successful vasectomy. Counselling on emergency contraception should also be provided. The male patient is also required to take a specific 5-question 'yes-no' quiz to assess his understanding of the requirements for taking the drug. The requirements for completing and signing an informed consent form and for completing a confidential survey enrolment form are the same for male patients as for female patients.

Following completion of the requirements of the STEPS programme, the prescriber may write a prescription for thalidomide. Prescriptions cannot be issued by telephone, and no more than a 4-week supply can be prescribed, with no automatic refills. All prescriptions are required to be filled within 7 days.

In subsequent visits, male patients are to be counselled again on the provisions of the STEPS programme. In addition, a follow-up survey form is required to be completed at each visit or at least once every 3 months during therapy. Subsequent prescriptions are required to specify no more than a 4-week supply of thalidomide for therapy.

3.2 Requirements for Pharmacists

The pharmacist also plays an essential role in preventing fetal exposure to thalidomide. All retail and hospital pharmacies must register with the Celgene Corporation before they can dispense thalidomide. Pharmacies may request a STEPS programme registration form and thalidomide order form by calling Celgene. The Head Pharmacist or Director of Pharmacy must sign the registration form and certify that the pharmacy will comply with all requirements of the STEPS programme.

Before dispensing thalidomide to a patient, pharmacists are required to collect the patient's informed consent form signed by both the patient and prescriber, along with a properly written prescription. Thalidomide cannot be dispensed if the prescription was written more than 7 days prior to presentation at the pharmacy. Completed informed consent forms should be retained at the pharmacy.

Before dispensing thalidomide, the pharmacist is required to verify patient eligibility by calling the STEPS Patient Registry and entering specified information, including the final 6 digits of the patient's social security number. After patient eligibility has been verified, the pharmacist can dispense the drug. The drug is required to be dispensed in intact blister packs containing 14 capsules each. Each blister pack is printed with a warning about severe birth defects and other adverse effects from thalidomide use. A symbol behind and on each capsule is intended to convey the meaning 'do not get pregnant,' and a photograph of a baby with severe limb defects caused by thalidomide ex-

posure during pregnancy is also included in the package. Each blister pack contains a package insert with a boxed warning that if thalidomide is taken during pregnancy, it can cause severe birth defects or death to an unborn baby, and should never be used by women who are pregnant or who could become pregnant while taking the drug. The warning states that even a single dose (a 50mg capsule) can cause severe birth defects. Three additional boxed warnings directed to prescribers, female patients and male patients contain special information about the restrictions on thalidomide distribution and use specified by the STEPS programme.

Pharmacists are directed not to repackage thalidomide capsules. When subsequent prescriptions are presented by a patient, patient eligibility should again be verified before the prescription is filled. No more than 7 days may remain on the previous prescription. The pharmacist is also required to accept the return of any thalidomide not used by a patient.

4. Can Birth Defects from Thalidomide Use be Prevented?

Thalidomide is now available for prescription use in the US, and is likely to be approved for prescription use in other countries in the future. There is much concern that use of the drug will increase substantially in the future and lead to another worldwide epidemic of thalidomide-induced birth defects. Thalidomide is currently available at leprosy treatment centres in 8 South American countries, and is commercially available at some pharmacies in Brazil.[23] 33 cases of thalidomide embryopathy have already been reported in the literature in Brazil.[23] In 11 of these cases a full description of the pregnancy was available, and in each case the mother took thalidomide during pregnancy for treatment of leprosy. The investigators attributed these cases of thalidomide embryopathy to the high prevalence of leprosy in Brazil, the high rate of unintended pregnancies, the low commercial cost of thalidomide and more relaxed drug control measures.

In addition to the treatment of erythema nodosum leprosum, thalidomide has been shown to be effective in treating aphthous ulcers in patients with AIDS.[24] If it also proves to be effective in the treatment of rheumatoid arthritis, severe bodyweight loss in patients with AIDS, graft-versus-host disease, neoplasms, diabetic retinopathy, macular degeneration or other prevalent diseases, it could potentially be used by millions of patients each year. Since the mid 1960s, few cases of thalidomide embryopathy have been reported in the literature because thalidomide has been used only for treatment of erythema nodosum leprosum in countries where leprosy is endemic, or else it has been used as an investigational drug in a limited number of patients with stringent precautions taken to prevent fetal exposure. However, should the drug be approved for prescription use in several countries to treat any of the above conditions, or should it become widely used to treat non-approved indications, many more cases of thalidomide embryopathy could occur.

What is the likelihood that regulatory programmes such as the Celgene STEPS programme can prevent another epidemic of thalidomide-induced birth defects? The mandatory STEPS programme for thalidomide has the potential to be a major improvement over the voluntary Pregnancy Prevention Program for isotretinoin. If the programme functions as designed, it could be highly effective at preventing fetal exposures to thalidomide. However, the programme has been in operation for only a few months, and it is too early to determine how successful it will actually be. The effectiveness of the STEPS programme will depend upon how well patients, prescribers and pharmacists comply with its mandates. Lack of full compliance with the directives of the programme could result in fetal exposures to thalidomide. It is unlikely that many fetal exposures to thalidomide will occur from treatment of erythema nodosum leprosum in the US, because fewer than 500 US women with childbearing ability have the form of leprosy that puts them at risk for developing erythema nodosum leprosum (US Hansen's Disease Center, personal

communication). However, if the drug is approved for treatment of more prevalent diseases such as AIDS and cancer, or if use for non-approved indications becomes common, many more women with childbearing ability could be treated by the drug. Even with the safeguards present in the STEPS programme, it is likely that some fetal exposures to thalidomide will eventually occur, resulting in fetal deaths, elective termination of pregnancies or the birth of infants with serious defects that cause lifelong disability.

The greatest danger of large numbers of pregnant women being exposed to thalidomide may arise from the distribution of the drug by manufacturers in countries where the availability and use of the drug is less regulated, or through black market sources in countries where the drug is tightly regulated. Adverse economic conditions and the ability to obtain the drug from less expensive sources with fewer requirements than the STEPS programme could potentially defeat much of the protection against fetal exposure offered by the STEPS programme. In the US, the FDA hopes that controlled availability of thalidomide by prescription will undermine availability of the drug on the black market. However, should thalidomide be widely used in countries where it is available at low cost with few, if any, government restrictions on its distribution and use, the potential for thalidomide-affected pregnancies could be very high. Even if a country tightly regulates the distribution and use of thalidomide, poor economic conditions or the unwillingness or inability of patients or prescribers to comply with strict regulations governing its use could motivate patients to seek the drug from other sources. There is, therefore, the potential for another epidemic of thalidomide-related birth defects in underdeveloped countries or in countries where there is little, if any, control over availability and use of the drug. The magnitude of such an epidemic would still probably be less than the epidemic of the late 1950s and early 1960s when thalidomide was widely used to treat morning sickness among pregnant women.

If the STEPS programme proves to be effective at preventing fetal exposure to thalidomide, we recommend that it or similar programmes be approved by the regulatory authorities in all countries where the drug will be used in the future. Regulatory authorities should also consider using components of the STEPS programme as a model for the regulation of other known human teratogens that are available on the market.

The most desirable way to prevent birth defects from thalidomide use is to develop nonteratogenic analogues of the drug that are at least as effective as thalidomide in treating serious diseases. Celgene is presently developing and testing several analogues of thalidomide that show promise in treating serious illnesses. Many of these drugs do not appear to be teratogenic in preliminary testing with laboratory animals (Celgene Corporation, personal communication). Development of these drugs should be a high priority and should be encouraged by regulatory authorities such as the FDA.

5. Conclusions

Thalidomide is effective in treating erythema nodosum leprosum in leprosy patients and aphthous ulcers in patients with AIDS. It also shows promise in treating many other diseases. If the drug should be approved in the future for treatment of diseases with high prevalence such as AIDS and cancer, hundreds of thousands of women with childbearing ability could take the drug. The STEPS programme mandated by the FDA promises to be effective in preventing fetal exposures to the drug as long as patients, prescribers and pharmacists comply with all of the provisions of the programme. However, the actual effectiveness of the STEPS programme has not been determined, and it is not certain that the STEPS programme, or similar programmes, will be required in other countries where thalidomide may become available. Even if all countries were to require close regulation of thalidomide similar to the STEPS programme, some pregnancies would probably occur during treatment, leading to death of the fetus, elective termination of the pregnancy or additional

cases of serious birth defects among liveborn infants. Should thalidomide be used extensively in countries where distribution and use of the drug is not tightly regulated, another epidemic of thalidomide-induced birth defects could occur.

The most desirable and effective way to prevent thalidomide-induced birth defects is to eliminate the need for thalidomide. We recommend that development of nonteratogenic analogues of thalidomide be encouraged and supported so that the tragic results of thalidomide use during pregnancy will never again be repeated.

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