

New Drugs

S.T.E.P.S.[™] : A Comprehensive Program for Controlling and Monitoring Access to Thalidomide

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ABSTRACT

In July 1998, the US Food and Drug Administration approved the marketing of thalidomide for the treatment of cutaneous manifestations of erythema nodosum leprosum. To ensure that fetal exposure to this teratogenic agent does not occur, the manufacturer has instituted a comprehensive program to control prescribing, dispensing, and use of the drug. This program, known as the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.[™] [Celgene Corporation, Warren, New Jersey]), is based in part on experience gained with other drugs—specifically isotretinoin and clozapine—that offer important clinical benefits but carry the potential for serious harm. To achieve its goal of the lowest possible incidence of drug-associated teratogenicity, the S.T.E.P.S.[™] program uses a three-pronged approach: (1) controlling access to the

drug; (2) educating prescribers, pharmacists, and patients; and (3) monitoring compliance. Clinicians who wish to prescribe thalidomide must be registered in the S.T.E.P.S.[™] Prescriber Registry and agree to prescribe the drug in accordance with S.T.E.P.S.[™] patient eligibility criteria and monitoring procedures. Pharmacies must also register and agree to comply with patient identification and monitoring criteria. Finally, patients receive visual aids, including a videotape, written material, and verbal counseling about the benefits and risks of thalidomide therapy, the importance of not becoming pregnant during therapy, and the types of contraception required (including emergency contraception) and their availability. Women of childbearing potential must agree to undergo pregnancy testing before starting therapy and on a regular schedule during therapy. All patients must agree to complete a confidential survey about their

compliance with contraception, testing, and drug therapy. The manufacturer is monitoring survey results and outcome data and is prepared to make whatever modifications to the S.T.E.P.S.[™] program are necessary to ensure its effectiveness. In addition to minimizing the potential risk for fetal harm associated with thalidomide therapy, the S.T.E.P.S.[™] program may provide a model for future cases in which a drug offers compelling benefits but poses profound risks unless its distribution is carefully controlled. **Key words:** congenital abnormalities, teratogenicity, thalidomide, patient education, prevention.

INTRODUCTION

For the first time, thalidomide is being sold commercially for clinical use in the United States. In July 1998, the US Food and Drug Administration (FDA) approved thalidomide* for the treatment of cutaneous manifestations of moderate-to-severe erythema nodosum leprosum (ENL) and as maintenance therapy for the prevention and suppression of ENL recurrence.¹

This latest development in the long history of the drug followed much debate over its benefits and risks and how, if at all, the risks can be managed.² Thalidomide is now available to those who require it, but as the FDA has stated, it is "among the most tightly restricted drugs to be marketed in the United States."¹ To reduce the risk of thalidomide-related teratogenicity to the absolute minimum, Celgene has developed a comprehensive program to control and monitor the drug's prescribing, dispensing, and use.

*Trademark: THALOMID[™] (Celgene Corporation, Warren, New Jersey).

The System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.[™] [Celgene Corporation, Warren, New Jersey]) is based partly on 2 existing models—the safety programs developed for isotretinoin and clozapine. However, the scope of the S.T.E.P.S.[™] program exceeds that of these earlier programs by incorporating additional mandatory controls and ongoing compliance monitoring and by establishing a set of interrelated databases and standard operating procedures that provide mechanisms for improving the program if deficiencies in its operation are detected. This article describes the organization of the S.T.E.P.S.[™] program; the roles of prescribers, pharmacists, and patients; and the structures and procedures in place for monitoring both participant compliance and the program's effectiveness in preventing fetal exposure to thalidomide.

A BRIEF HISTORY OF THALIDOMIDE

First marketed in 1956 in West Germany, thalidomide was widely sold outside the United States, most commonly as a sedative; it had a benign safety profile compared with that of barbiturates.³ By 1961, it was clear that use of thalidomide during pregnancy was associated with major congenital abnormalities. Withdrawal of the drug from markets followed, but approximately 12,000 infants worldwide were born with severe birth defects.⁴ Because the FDA had not yet approved the drug, in part out of concern about reported cases of peripheral neuropathy, thalidomide never reached the US market, and this country was largely spared the tragedy.²

In 1965, Sheskin⁵ reported use of thalidomide as a sedative in leprosy pa-

tients with ENL and indicated that the drug caused rapid and dramatic improvement in type II lepra reactions. Subsequent controlled studies confirmed the efficacy of the drug in the treatment of ENL.^{6,7} In addition to being used widely in the treatment of ENL, thalidomide has been and continues to be investigated for the treatment of various other conditions.⁸

THALIDOMIDE-ASSOCIATED TERATOGENICITY

Fetal abnormalities related to thalidomide therapy include amelia (congenital absence of limbs), phocomelia (shortened limbs), hypoplasticity of the bones, absence of bones, external ear and eye abnormalities, facial palsy, and congenital heart defects.⁹ A German retrospective study suggested that the greatest risk of teratogenicity occurs when thalidomide is ingested during the 34th to 50th day of pregnancy.¹⁰ However, it cannot be inferred from the historical data that there is any period of pregnancy during which thalidomide administration is safe, nor is there any level of exposure during pregnancy at which the drug is known to be safe. For example, a single exposure to a 100-mg dose was determined to cause malformations.¹¹

EXPERIENCE IN MANAGING SPECIAL DRUG-ASSOCIATED RISKS

Isotretinoin

In the past 2 decades, clinicians and the pharmaceutical industry have gained experience in the use of drugs that offer important clinical benefits but carry poten-

tially serious risks. Teratogenicity has been addressed in the case of isotretinoin,* an oral drug capable of producing prolonged remissions in patients with severe, recalcitrant cystic acne.¹² In 1988, after receiving reports of retinoic acid-induced embryopathy, the manufacturer of isotretinoin implemented a program designed to allow female patients access to the drug while minimizing the teratogenic hazard.¹³

In contrast to the case of thalidomide, retinoic acid's teratogenic effect was known before marketing; the initial labeling of isotretinoin included a warning against use during pregnancy. Nonetheless, reports of birth defects and spontaneous abortions appeared in women exposed to isotretinoin during the first trimester of pregnancy.¹² The reports mounted despite warnings to physicians through direct mailings, advertisements, and the package insert; by 1989, 78 malformed infants had been born to women taking isotretinoin.¹¹

The FDA and the manufacturer of isotretinoin redoubled their efforts to alert physicians and patients to the teratogenic effects of the drug. In addition, the manufacturer implemented a variety of educational programs and made changes in labeling and packaging.¹² In 1988 the labeling was revised to state that isotretinoin therapy is contraindicated in women capable of becoming pregnant, with the exception of those with severe, disfiguring nodular acne that is unresponsive to standard therapies. In addition, women who are candidates for isotretinoin therapy must be judged capable of complying with therapy and taking contracep-

*Trademark: Accutane® (Roche Pharmaceuticals, Nutley, New Jersey).

tive measures, must be given verbal and written warnings of the teratogenic hazard, and must have a negative result on a serum or urine pregnancy test within 14 days of starting therapy.

The manufacturer also instituted the Pregnancy Prevention Program to encourage attention to the above requirements.¹³ This program comprises a kit containing educational material for patients, a standard patient consent form, and checklists for both the patient and physician to verify that the patient meets the criteria for therapy with isotretinoin. Awareness of the program has been reinforced by periodic communications to prescribers and pharmacists. The elements of the program that depart from usual medical practice include: (1) a formalized process for ensuring informed patient consent, (2) a provision by the manufacturer to reimburse patients for the cost of contraceptive counseling, and (3) the requirement that women use the drug solely for its labeled indication. Later the manufacturer repackaged isotretinoin in a 10-capsule blister pack containing information directed specifically at women: a warning about the risks of becoming pregnant while taking isotretinoin or during the month after treatment, an "avoid pregnancy" icon on each capsule, and line drawings of malformations associated with the drug.

In 1995, Mitchell and coworkers,¹³ from the Slone Epidemiologic Unit (SEU) at the Boston University School of Medicine School of Public Health, reported that women receiving isotretinoin under the Pregnancy Prevention Program had a substantially lower pregnancy rate than the general population: 8.8 versus 109 per 1000 person-years. In addition, 24,258 (99%) of 24,503 women interviewed within 1 month of enrollment in the pro-

gram said that they had been told to avoid pregnancy. Further, posttherapy tracking showed that pregnancy rates increased in the 4 months after cessation of isotretinoin therapy, which is consistent with avoidance of pregnancy during the period of teratogenic risk.

Clozapine

A different challenge was posed by the antipsychotic agent clozapine.* The drug benefited patients with schizophrenia who did not respond to other medications by improving negative as well as positive symptoms of the disease.^{14,15} Unfortunately, clinical research findings and foreign postmarketing experience indicated that 1% to 2% of patients developed agranulocytosis, which is potentially fatal.¹⁶ At the same time, however, the data showed that none of the patients whose agranulocytosis was detected through laboratory tests died before they developed infection. This suggested that patient surveillance could help prevent agranulocytosis.¹⁶

The FDA's approval of the drug in 1989 was contingent on such surveillance, and the manufacturer created the Clozaril National Registry, a program designed to register treating physicians and patients, ensure patient monitoring (regular blood testing), and limit distribution of the drug to compliant individuals. All patients who received clozapine were required to have a white blood cell count at baseline and weekly thereafter until 4 weeks after the end of treatment. Patients could receive medication only when data on their white blood cell count were current. The registry system also provided guidelines for

*Trademark: Clozaril™ (Sandoz Pharmaceuticals, Hanover, New Jersey).

physicians, pharmacies, patients, the manufacturer, and distributors to ensure proper use of the medication. Clozapine could be distributed only by registered pharmacies that agreed to follow the "no blood-no drug" guideline of the registry.¹⁷

A review of 5 years' data from more than 99,000 patients in the registry showed that the incidence of agranulocytosis was significantly lower than expected (0.38% vs the expected 1% to 2%). As a result of the success of the program, the FDA recently approved a modification of the white blood cell count-monitoring regimen: Now patients must undergo weekly blood monitoring for the first 6 months of continuous clozapine therapy (when the risk for agranulocytosis is highest), followed by bi-weekly blood tests for patients with no evidence of hematologic abnormalities.

OBJECTIVES AND ORGANIZATION OF S.T.E.P.S.TM

Celgene Corporation has incorporated elements of both these successful programs into the S.T.E.P.S.TM program for controlling the distribution of thalidomide. Educational materials for patients and physicians and label warnings similar to those

used in the isotretinoin program are coupled with clinician and patient registration and testing similar to those used in the clozapine program.

The S.T.E.P.S.TM program is multifocal—directed at prescribers, pharmacists, and both male and female patients. Its goal is straightforward: to ensure that fetal exposure to thalidomide does not occur. The methods that are being used to accomplish this goal are outlined in Table I.

A team approach is necessary. Program implementation and oversight are performed by Celgene, the SEU, and the Celgene S.T.E.P.S.TM Management Committee. The management committee has overall responsibility for monitoring and auditing the program. The committee is composed of at least 7 persons, including senior Celgene personnel in the medical affairs, regulatory, and drug safety departments, and industry experts with expertise in computerized databases, warehousing and distribution, manufacturing procedures, compliance auditing, and other areas. The SEU has a separate advisory board composed of representatives of various interest groups (eg, the Thalidomide Victims Association of Canada and the March of Dimes), experts in the use of thalidomide

Table I. Methods of accomplishing the goal of the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.TM).

Maintenance of electronic databases of registered and compliant prescribers, pharmacists, and patients to control access to drug.

Education of prescribers, pharmacists, and patients about the risks associated with thalidomide therapy and the requirement for adequate contraceptive measures and pregnancy testing for women of childbearing potential.

Continuous compliance monitoring through mandatory patient surveys, reports to a central management committee, and regular system-wide audits.

for treating various medical conditions, and epidemiologists.

Celgene's primary responsibilities include providing potential prescribers and dispensers with S.T.E.P.S.™ program materials and supplying educational materials and drug. The company had prepared a variety of educational materials in anticipation of FDA approval of thalidomide, including patient-oriented videotapes, discussing the risks associated with the drug to ensure responsible prescribing and dispensing and to enhance patient compliance. These are being supplied directly to all registered prescribers and pharmacies. (Persons interested in receiving some of these materials can call 1-888-4-CELGENE.) In addition, Celgene is sending monthly letters to prescribers that highlight prescribing and counseling requirements for thalidomide.

Celgene is providing thalidomide only to pharmacies that are registered and comply with S.T.E.P.S.™ requirements. The company has designed, constructed, and currently maintains the Pharmacy Dispensing Registry, which comprises data on prescribing, dispensing, and distribution. These data are being constructed from registration cards returned by prescribers; registration cards, dispensing information, and drug orders from pharmacies; and patient registration forms. Celgene is providing pharmacists with on-line and toll-free telephone access to prescriber, pharmacist, and patient eligibility information. Using this on-line registry, pharmacists must verify that program requirements have been met. Celgene is providing pharmacy dispensing data to SEU on a monthly basis for compliance tracking and quality assurance monitoring.

The SEU brings to the S.T.E.P.S.™ program experience in patient-compliance

surveying from the Accutane Pregnancy Prevention Program. By reviewing the mandatory confidential survey completed by both prescribers and patients, SEU is monitoring compliance with the educational, informed consent, and pregnancy-testing components of the program.

The S.T.E.P.S.™ Management Committee is charged with overseeing the entire process and making certain that it is working. This entails timely transfer of information from the distribution database to the SEU database; timely investigation and resolution of any concerns about prescriber, pharmacy, or patient compliance with the program; and making recommendations to the FDA for changes in the program based on real-time data.

The committee is chaired by the company president. The senior regulatory individual is the principal liaison with the FDA for company responses to the agency's inquiries. The S.T.E.P.S.™ manager, who reports to the president, oversees the initial and follow-up audit to determine whether distribution is in accordance with S.T.E.P.S.™ program policy and procedures; this individual also monitors continuing reviews of standard operating procedures by Celgene and SEU. The thalidomide product manager helps monitor the program's effectiveness (eg, through communications with field-based Celgene representatives) and will implement recommendations made by the committee relating to the sale and promotion of the drug. Medical affairs and drug safety personnel on the committee serve as liaisons with health care providers and SEU and are responsible for ensuring appropriate professional education on the risks of fetal exposure to thalidomide and the means of preventing it and for capturing reports of any adverse experiences.

THE REGISTRATION PROCESS

Prescribers

Initially, those who are most likely to prescribe thalidomide are being sent information about the S.T.E.P.S.[™] program. On request, these prescribers and others who express interest will receive a S.T.E.P.S.[™] folder with a registration card and an educational monograph. Clinicians who are interested in prescribing thalidomide must register in the program.

The registration card outlining the terms of prescribing must be signed by the prescriber and returned to Celgene. To participate in the S.T.E.P.S.[™] program, the prescriber must agree to: (1) provide comprehensive patient counseling on the benefits and risks of thalidomide, as outlined in the informed consent form; (2) provide appropriate contraception counseling and pregnancy testing; (3) submit completed informed consent forms to SEU; (4) complete the prescriber portion of the patient-monitoring survey and return the document to SEU; (5) prescribe a quantity of drug no greater than is required for 28 days of therapy, with no refills; and (6) encourage patients to return unused thalidomide to their pharmacy. The registrant does not become eligible to prescribe until Celgene has entered all the prescriber registration information in the prescriber database.

Pharmacies

Retail and hospital pharmacies must also register to dispense thalidomide. The head pharmacist of each pharmacy (or the director of pharmacy at a hospital) takes responsibility for registering and for educating other members of the staff about the S.T.E.P.S.[™] program. Pharmacies interested in registering may contact Celgene.

Like prescribers, pharmacies must agree to the terms of the S.T.E.P.S.[™] program. Their participation in the program involves: (1) collecting and filing the patient's signed informed consent form with the initial prescription; (2) registering thalidomide recipients by fax or telephone; (3) dispensing no more than 28 days of thalidomide therapy, with no refills (hospitals will usually dispense a 7-day supply); (4) verifying patient registration and recording subsequent prescriptions on-line or by telephone; (5) accepting and storing (or returning to Celgene) any unused thalidomide returned by patients; and (6) informing all staff pharmacists of the dispensing procedure for thalidomide. The pharmacy registration card outlining the terms for dispensing must be signed by the pharmacist and returned to Celgene.

All registration data provided by the pharmacy are entered into the dispensing database by the distributor. The pharmacy is then designated eligible to dispense, and a monograph is mailed to the pharmacist.

Patients

Patient registration forms are completed by the pharmacist and sent to Celgene for entry into the distribution database. The pharmacist registers patients only if the patient presents a copy of the S.T.E.P.S.[™] informed consent document signed both by the patient and a registered prescriber and a prescription written by the prescriber.

PRESCRIBING AND DISPENSING

Under the S.T.E.P.S.[™] program, the prescriber counsels patients about the benefits and risks of thalidomide therapy and provides patients with the literature and

videotape. All materials that are necessary for compliance with the program requirements are contained in the S.T.E.P.S.[™] folder (Table II). Various educational materials for facilitating the informed consent process are included. The contents of 1 folder should be used with 1 patient only and kept with the patient's medical record.

It is crucial that the prescriber gauge the patient's understanding of the risks of thalidomide treatment and the requirements for eligibility for treatment. To facilitate this, a brief quiz is included with the S.T.E.P.S.[™] materials. If the patient cannot answer all questions on this quiz

correctly, the prescriber is urged to review the materials with the patient and assess whether the patient is a suitable candidate for the program. The patient must be able to answer all questions correctly to enter the program.

To receive thalidomide, women of childbearing potential must agree to use 2 reliable forms of contraception, with the sole exception of women who agree to abstain from sexual intercourse with men. Only women who have undergone hysterectomy, who are postmenopausal, or who have had no menses for at least 24 consecutive months are considered incapable of childbearing. The prescriber must

Table II. Program materials for the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.[™])*

1. Registration card. The prescriber completes this and returns it to the distributor.
 2. Instructions for prescribers. These describe how the S.T.E.P.S.[™] program is implemented.
 3. Patient referral form. This can be used to refer patients to another health care provider for contraceptive counseling or pregnancy testing.
 4. *Important Information for Men and Women Taking THALOMID[™] (Thalidomide)*. This pamphlet explains the reproductive hazards of the drug (it includes a photograph of an infant with severe birth defects), other adverse effects, and requirements for becoming and remaining eligible for treatment. On the front page of the pamphlet, there is the warning, "If thalidomide is taken during pregnancy, it causes severe birth defects or death to the unborn baby. Thalidomide should never be used by women who are pregnant or could become pregnant." The pamphlet is available in English and 14 other languages.
 5. *Your Contraceptive Choices*. This patient-education pamphlet, developed by Planned Parenthood, discusses the effectiveness, advantages, and disadvantages of various methods of contraception, including abstinence. It is available in English or Spanish.
 6. *Emergency Contraception*. This pamphlet, also developed by Planned Parenthood, identifies situations in which emergency contraception may be necessary, discusses the medications employed in emergency contraception and their use, and reviews what the patient can expect immediately after use. It is available in English or Spanish.
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*Enclosed in each folder provided to clinicians who wish to prescribe thalidomide.

provide contraceptive counseling, including information on emergency contraception, to women who are capable of conceiving but do not agree to abstain from sexual activity with men. A prescriber who feels uncomfortable about doing so may refer the patient to a gynecologist or other practitioner; a form to facilitate referral is included in the S.T.E.P.S.[™] folder. Women must thoroughly understand the need to use 2 forms of contraception simultaneously, beginning 4 weeks before the start of therapy with thalidomide and continuing throughout therapy until 4 weeks after stopping therapy; if the patient chooses to be abstinent, she must remain so during this entire period. Contraceptive methods must include at least 1 highly effective method (eg, intrauterine device, hormone preparation, tubal ligation, or partner's vasectomy) and 1 additional effective method (eg, condom, diaphragm, or cervical cap). If hormonal contraception or an intrauterine device is medically contraindicated, 2 other effective or highly effective methods must be used.

Women must also agree to undergo pregnancy testing before and during therapy. Pregnancy testing is required weekly during the first month of use and monthly thereafter in women with regular menstrual cycles and every 2 weeks in women whose cycles are irregular. Tests must be performed in the prescriber's office or laboratory and satisfy a sensitivity of <50 mIU/mL. Pregnancy testing must also be performed if a patient misses her period or there is any abnormality in menstrual bleeding. If pregnancy does occur during treatment, the drug must be discontinued immediately, and the prescriber and patient must discuss the implications of the pregnancy. Under these conditions, the patient must be referred to a board-certified

obstetrician/gynecologist, who will have received training in reproductive toxicity. To encourage compliance with the pregnancy-testing requirement, it is recommended that female patients initially receive no more than a 1-week supply of thalidomide for each of the first 4 weeks.

Male patients enrolled in the S.T.E.P.S.[™] program receive written and oral warnings of the risk of possible contraception failure and the need to use condoms when having intercourse with women of childbearing age. It is unknown whether thalidomide is present in sperm or semen or whether such presence would impair fetal development.

Patients must also agree never to donate blood or share thalidomide with anyone, even if the other individual has similar symptoms. They are cautioned to keep the drug out of the reach of children. Finally, they must agree to participate in the patient survey.

Patients and prescribers must both sign a four-copy informed-consent form; 1 copy is retained for the prescriber's files, 1 is sent to SEU for inclusion in the database, 1 is kept by the patient, and 1 is presented to the pharmacy for filing. Informed consent forms are available in 15 languages. Patients and prescribers also complete a survey form that captures data on contraceptive use and the condition being treated, explains the survey's purpose, and stresses the survey's confidentiality.

The prescriber can write a thalidomide prescription after completing the informed consent process and, for women of childbearing potential, obtaining a negative result from a pregnancy test. As mentioned, patients present the prescription and a signed copy of the informed consent form to a pharmacist at a registered pharmacy. If a pharmacy is not registered, the registration process can be completed by tele-

phone and fax, and the drug is shipped for arrival at the pharmacy within 2 days.

The packaging for thalidomide reiterates warnings on teratogenicity and the requirements for pregnancy testing and contraception. The capsule itself bears a simple and direct warning: the silhouette of a pregnant woman on which a black circle with a slash is superimposed.

Once a patient is entered in the S.T.E.P.S.[™] distribution database, the prescriber is mailed monthly reminders of the counseling and pregnancy-testing requirements. Patients returning to the prescriber's office for subsequent prescriptions: (1) receive counseling about appropriate contraception and the adverse effects associated with thalidomide therapy; (2) have a pregnancy test (if the patient is a woman of childbearing potential); (3) complete the confidential survey form; and (4) receive a new prescription for no more than a 28-day supply of thalidomide. Subsequent prescriptions cannot be filled if >7 days of therapy remain on the previous prescription or if the prescription was written more than 7 days before being presented.

MONITORING OF OUTCOMES

In addition to the survey form at the initiation of treatment, patients receiving thalidomide and the clinicians who prescribe it must complete frequent brief follow-up survey questionnaires (once a month for female patients and once every 3 months for male patients). The survey includes questions on demographic characteristics, knowledge of the drug-related risk of teratogenicity, sexual activity, and use of contraception. The prescriber adds information on pregnancy testing. Information that would identify a participant is held in confi-

dence by SEU (with the exception that study records may be examined in confidence by FDA representatives).

SEU cross-references data from patient surveys with the pharmacy dispensing registry weekly for the first 3 months and monthly thereafter to verify accuracy. When deviations from S.T.E.P.S.[™] program procedures are found, SEU contacts prescribers or patients in a timely manner by fax, telephone, or mail. Triggers for such contacts include failure to receive a survey form after a known visit, indication on a survey form that a sexually active woman is not using adequate contraception, disclosure by a woman that she may be pregnant, a male patient's report that his partner may be pregnant, and failure of registered prescribers to give patients adequate counseling. SEU periodically forwards routine data summaries and information (with the exception of patient identity) to the S.T.E.P.S.[™] management committee and immediately informs Celgene of any pregnancies, suspected fetal exposures, or noncompliant prescribers.

Data from the pharmacy dispensing registry will be sampled by an external auditor for periodic audits to measure registered pharmacies' compliance with the program. Audits will confirm, for example, that the pharmacy has obtained informed consent from each patient to whom it dispenses the drug and that appropriate intervals have elapsed between prescriptions. Subsequent to the initial audit of prescriptions, a schedule for ongoing compliance monitoring is implemented.

Finally, the management committee is charged with monitoring the ongoing experience from reports prepared by Celgene and SEU, ensuring compliance with operating procedures. The committee may

require that patients, prescribers, and pharmacists be re-educated if they do not demonstrate an understanding of their responsibilities in the S.T.E.P.S.[™] program. The committee also reserves the right, in cases of serious or repeated noncompliance, to revoke a prescriber's, pharmacist's, or patient's registration. Without registration, the individual cannot prescribe, distribute, or receive thalidomide. As necessary, the committee may recommend changes in the S.T.E.P.S.[™] program to the FDA. These recommendations may be part of or in addition to the quarterly monitoring reports submitted to the agency as part of the normal drug-licensing process. Any possible fetal exposure is reported to the FDA as a serious adverse event.

Despite all the checks and balances in the S.T.E.P.S.[™] program, the system will work only if it makes intuitive sense to its participants and they adhere to program requirements. Before finalizing the design of the program, Celgene conducted market research in groups of physicians who were likely to prescribe thalidomide, patients who were likely to use the drug, and pharmacists. Discussion groups were conducted in several regions of the United States. When given a description of thalidomide's properties without being told the name of the drug, every group stated that the drug being described was similar to thalidomide. When asked to take 10 minutes to discuss and design a system for safe distribution of the drug to those who would benefit from it, every group outlined a plan similar to the S.T.E.P.S.[™] program. Finally, after being presented the rudiments of the S.T.E.P.S.[™] program, every group agreed that the program was acceptable as presented.

On the basis of this experience and comments received subsequently from various patient advocacy groups, public health officials, and professional groups, we believe that the S.T.E.P.S.[™] program makes sense and thus participants will accept and follow it. Every person who comes in contact with a lawfully prescribed formulation of thalidomide will understand the drug's risks and should behave in a manner that will ensure prevention of fetal exposure.

CONCLUSIONS

Thalidomide carries a unique risk along with its important benefits, and a unique approach to managing this risk is necessary. Successful programs previously developed for isotretinoin and clozapine provided guides. However, the S.T.E.P.S.[™] program has a greater scope, combining intensive, continuing patient and professional education with restricted distribution and pregnancy testing. It also provides mechanisms for close, constant monitoring to quickly identify noncompliance or other problems. Celgene is committed to making the S.T.E.P.S.[™] program succeed and will make any modifications to the program that are necessary to ensure its effectiveness.

Future cases are certain to arise in which a drug offers compelling clinical benefits, but unrestricted distribution poses profound risks to patients or society. It is hoped that the S.T.E.P.S.[™] program will provide a model for resolving this recurring dilemma.

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REFERENCES

1. US Food and Drug Administration. FDA Approves Thalidomide for Hansen's Disease Side Effect, Imposes Unprecedented Restrictions on Distribution. Rockville, Md: National Press Office; July 16, 1998. Talk paper.
2. *Thalidomide: Potential Benefits and Risk*. Transcript of Open Public Scientific Workshop. Bethesda, Md: National Institutes of Health; 1997.
3. Mellin GW, Katzenstein M. The saga of thalidomide. Neuropathy to embryopathy, with case reports of congenital abnormalities. *NEJM*. 1962;267:1184-1193.
4. Gardner-Medwin JM. Thalidomide in autoimmune conditions. *Exp Opin Invest Drugs*. 1996;5:829-841.
5. Sheskin J. Thalidomide in the treatment of lepra reactions. *Clin Pharmacol Ther*. 1965;6:303-306.
6. Sheskin J, Convit J. Results of a double-blind study on the influence of thalidomide on the lepra reaction. *Int J Lepr*. 1969;37:135-146.
7. Iyer CGS, Languillon J, Ramanuja K, et al. WHO co-ordinated short-term double-blind trial with thalidomide in the treatment of acute lepra reactions in male lepromatous patients. *Bull WHO*. 1971;45:719-732.
8. Calabrese L, Resztak K. Thalidomide revisited: Pharmacology and clinical applications. *Exp Opin Invest Drugs*. 1998;7:2043-2060.
9. Mellin G, Katzenstein M. The saga of thalidomide (concluded). *NEJM*. 1962;267:1238-1244.
10. Lenz VW, Knapp K. Die Thalidomid-Embryopathie. *Dtsch Med Wochenschr*. 1962;87:1232-1242.
11. Gunzler V. Thalidomide in human immunodeficiency virus (HIV) patients. A review of safety considerations. *Drug Saf*. 1992;7:116-134.
12. Stern RS. When a uniquely effective drug is teratogenic. The case of isotretinoin. *NEJM*. 1989;320:1007-1009.
13. Mitchell AA, Van Bennekom CM, Louik C. A pregnancy-prevention program in women of childbearing age receiving isotretinoin. *NEJM*. 1995;333:101-106.
14. Kane JM, Honigfeld G, Singer J, and the Clozaril Study Group. Clozapine for the treatment-resistant schizophrenic: Results of a US multicenter trial. *Psychopharmacology*. 1989;99:S60-S63.
15. Kane JM, Honigfeld G, Singer J, and the Clozaril Study Group. Clozapine for the treatment-resistant schizophrenic: A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. 1988;45:789-796.
16. Reducing clozapine-related morbidity and mortality: 5 Years of experience with the Clozaril National Registry. *J Clin Psychiatry*. 1998;59(Suppl 3):3-7.
17. Honigfeld G. Effects of the Clozapine National Registry System on incidence of deaths related to agranulocytosis. *Psychiatr Serv*. 1996;47:52-56.