New Drugs

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

Jerome B. Zeldis, MD, PhD,[1] Bruce A. Williams,[2] Steve D. Thomas, PhD,[3] and Marc E. Elsayed[2]

Departments of [1]Medical Affairs, [2]Sales and Marketing, and [3]Immunotherapeutics, Celgene Corporation, Warren, New Jersey

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

0149-2918/99/$19.00

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, Sheskin[5] reported use of thalidomide as a sedative in leprosy patients with ENL and i
drug caused rapid an
provement in type II
Subsequent controlled s
the efficacy of the drug
of ENL.[6,7] In additio
widely in the treatment
mide has been and cont
tigated for the treatmen
conditions.[8]

THALIDOMIDE-ASS
TERATOGENICITY

Fetal abnormalities relat
therapy include amelia
sence of limbs), phoco
limbs), hypoplasticity
sence of bones, externa
normalities, facial pals
heart defects.[9] A Germ
study suggested that th
teratogenicity occurs wh
ingested during the 34t
pregnancy.[10] However,
ferred from the historica
any period of pregnan
thalidomide administrati
there any level of expo
nancy at which the dru
safe. For example, a sin
100-mg dose was dete
malformations.[11]

EXPERIENCE IN MA
SPECIAL DRUG-ASS
RISKS

Isotretinoin

In the past 2 decades, pharmaceutical industry
perience in the use of dr
portant clinical benefits

domide Education S.T.E.P.S.™ [Cel-en, New Jersey]) sting models—the d for isotretinoin the scope of the ceeds that of these orporating addi-ols and ongoing and by establish-l databases and edures that pro-nproving the pro-ts operation are scribes the orga-S.™ program; the macists, and pa-s and procedures both participant ram's effective-al exposure to

F

West Germany, sold outside the only as a seda-ty profile com-rates.[3] By 1961, it idomide during with major con-ithdrawal of the d, but approxi-dwide were born Because the FDA rug, in part out cases of periph-de never reached ntry was largely

eported use of 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 potentially 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 program 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 infections. 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 physicians, pharmacies, pa
ufacturer, and distributors
use of the medication. Clo
distributed only by registe
that agreed to follow the
drug" guideline of the reg

A review of 5 years' c
than 99,000 patients in the
that the incidence of agra
significantly lower than e
vs the expected 1% to 2%
the success of the progra
cently approved a modifica
blood cell count–monitorin
patients must undergo wee
itoring for the first 6 montl
clozapine therapy (when th
ulocytosis is highest), fo
weekly blood tests for pati
idence of hematologic abn

OBJECTIVES AND ORGANIZATION OF S.

Celgene Corporation has i
ements of both these succe
into the S.T.E.P.S.™ progr
ling the distribution of tha
cational materials for pati
cians and label warnings

Table I. Methods of acc
and Prescribing

Maintenance of electronic da
patients to control access to d
Education of prescribers, pha
therapy and the requirement f
women of childbearing poten
Continuous compliance moni
agement committee, and regu

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

had been told to avoid
posttherapy tracking
ucy rates increased in
ssation of isotretinoin
nsistent with avoid-
during the period of

ge was posed by the
clozapine.* The drug
ith schizophrenia who
ther medications by
as well as positive
lisease.[14,15] Unfortu-
ch findings and for-
experience indicated
ients developed agran-
otentially fatal.[16] At
ever, the data showed
ents whose agranulo-
through laboratory
developed infections.
patient surveillance
anulocytosis.[16]
al of the drug in 1989
uch surveillance, and
ted the Clozaril Na-
gram designed to reg-
ians and patients, en-
ing (regular blood
stribution of the drug
uals. All patients who
re required to have
ount at baseline and
til 4 weeks after the
ients could receive
n data on their white
re current. The reg-
ided guidelines for

ndoz Pharmaceuticals,

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 biweekly blood tests for patients with no evidence of hematologic abnormalities.

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

Celgene Corporation has incorporated elements of both these successful programs into the S.T.E.P.S.™ 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.™ 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.™ 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.™).

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.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.