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Thalidomide Use in the US

Experience with Pregnancy Testing in the S.T.E.P.S.® Programme

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Abstract

Introduction: In 1998, thalidomide (Thalomid®), a known human teratogen, was approved by the US FDA for the treatment of erythema nodosum leprosum. To prevent fetal exposure to thalidomide, a restricted distribution risk management programme, the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.®), was implemented. All clinicians, pharmacists and patients who prescribe, dispense and receive thalidomide, respectively, are required to enrol in S.T.E.P.S.®. Sexually active females of childbearing potential must use two methods of birth control before, during and after treatment. These patients must also have a negative pregnancy test within 24 hours before beginning therapy and periodically while on therapy. The objective of this report is to summarise the patterns of thalidomide use and to describe the occurrence of positive pregnancy tests in females of childbearing potential while they were using thalidomide in the S.T.E.P.S.® programme in the US.

Study design/methods: A retrospective review of patients receiving thalidomide within the S.T.E.P.S.® programme from September 1998 to 31 December 2004 to determine the occurrence of positive pregnancy tests whilst on treatment.

Results: Approximately 124 000 (43% female) patients were registered within the S.T.E.P.S.® programme between September 1998 and 31 December 2004. Approximately 6000 patients were females of childbearing potential, representing 5% of all patients and 11% of all female patients. Between 30 July 2001 and 31 December 2004, >88% of thalidomide use was for oncological conditions. There were 72 females of childbearing potential who had positive pregnancy tests. Sixty-nine of these patients had false positive pregnancy tests. Of the remaining three, one woman was pregnant while on thalidomide. This patient had an initial negative test and received thalidomide. Therapy was stopped when she had a positive pregnancy test. This pregnancy resulted in a miscarriage. Two additional patients were determined to be pregnant before receiving thalidomide.

Conclusions: The S.T.E.P.S.® programme is critical to managing the risks of thalidomide-associated teratogenicity. Sustained vigilance among healthcare providers and patients receiving thalidomide is essential to its continued success.

Healthcare providers should be aware of the occurrence of false-positive pregnancy tests in females of childbearing potential receiving thalidomide.

Introduction

Thalidomide first became available in 1956 in West Germany as a sedative-hypnotic agent. By 1960 it had been introduced in 46 countries (excluding the US) and was widely used to treat nausea and vomiting in early pregnancy. An epidemic of phocomelia, an extremely rare congenital abnormality of the limbs, and other associated malformations in an estimated 15 000 babies soon followed.[1] Germany withdrew thalidomide from its market in November 1961 and other countries followed over the next 10 months.

In 1998 the Thalomid® [1] brand of thalidomide (Celgene Corporation, Summit, NJ, USA), was approved by the US FDA to treat erythema nodosum leprosum. Thalidomide is marketed in three countries outside of the US by the Pharmion Corporation through an international licensing agreement with Celgene. These three countries include Australia, New Zealand and Turkey. There are other companies worldwide that market and distribute other dose presentations of thalidomide; not all of these have risk management programmes.

To prevent fetal exposure to thalidomide, a risk management programme, the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.®), was implemented in the US, and a similar programme was implemented internationally by Pharmion. All clinicians, pharmacists and patients who prescribe, dispense and receive Thalomid®, respectively, are required to enrol in this restricted distribution programme, regardless of the disease that is being treated.[2] The S.T.E.P.S.® programme is an intensive, multi-component, integrated risk management programme that restricts drug use to registered clinicians, pharmacists and patients (figure 1).

The purpose of the present study is to summarise the patterns of thalidomide use in the US and to describe the cases of positive pregnancy tests that have occurred in females of childbearing potential. This report is a summary of the programme review of registered patients receiving Thalomid® in the mandatory S.T.E.P.S.® programme in the US.

Study Design and Methods

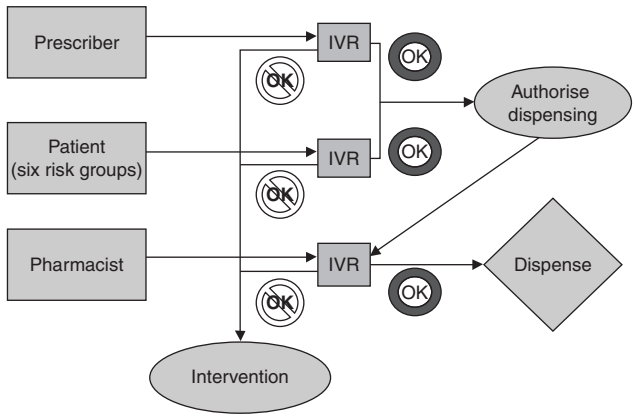
A retrospective review was conducted of patients in the Celgene database who received Thalomid® in S.T.E.P.S.® from September 1998 to 31 December 2004, including a more in-depth review of all patients who had positive pregnancy tests. Patient identifiers were removed for this S.T.E.P.S.® programme evaluation. This research was reviewed and approved by the FDA Research Involving Human Subjects Committee. Descriptive characteristics of all patients with positive pregnancy tests were evaluated including patient demographics, the reason for thalidomide treatment, concomitant medications used and concomitant diseases present.

Females of childbearing potential were defined as postmenarchal women who had not undergone a hysterectomy or who had not been naturally postmenopausal for at least 24 consecutive months (i.e. who have had menses at some time in the preceding 24 consecutive months), in accordance with the Thalomid® product labelling.[3]

All positive pregnancy tests were further evaluated by the patient's healthcare provider using any of the following: serial β-human chorionic gonadotropin (β-hCG) testing, serum hormone testing (e.g. luteinising hormone, follicle-stimulating hormone, estradiol), medical history, physical evaluation, pelvic ultrasound and/or gynaecological consultation according to standard operating procedures adjusted as clinically appropriate. A true-positive pregnancy

1 Thalomid® and S.T.E.P.S.® are registered trademarks of Celgene Corporation. The use of trade names is for product identification purposes only and does not imply endorsement.

test was defined as a positive pregnancy test in a female who was confirmed to be pregnant based upon further evaluation with the aforementioned tests or procedures. A false-positive pregnancy test was defined as a positive pregnancy test in a female who was found not to be pregnant based upon follow-up evaluation. The overall category of false positive pregnancy tests included indeterminate α-hCG test results.



Prescriber: A licensed practitioner and registered in *S.T.E.P.S.*®. The prescriber calls the interactive voice response (IVR) system and responds to a brief series of questions, including the amount of thalidomide (Thalomid®) to be dispensed.

Patient: A person registered within *S.T.E.P.S.*® and able to receive thalidomide. The patient calls the IVR system and responds to a brief series of questions designed to query the patient on procedures to assure safe use of thalidomide.

Pharmacist: A pharmacy registered with *S.T.E.P.S.*® who will dispense thalidomide. The pharmacist calls the IVR system to check if the thalidomide prescription has been authorised (i.e. the physician's and the patient's responses to the IVR queries are in accordance with the parameters for safe use of thalidomide) and enter quantity to be dispensed.

IVR: A telephone-based system used by patients and prescribers to complete required surveys and for pharmacists to receive verification to dispense thalidomide. The IVR verifies that females of childbearing potential are using two methods of birth control, at least one of which is designated as a highly effective method, unless the woman completely abstains from heterosexual sexual contact. The methods of birth control must be initiated 4 weeks prior to beginning thalidomide and the woman must have a negative pregnancy test within 24 hours before the first dose of thalidomide. All females of childbearing potential must have pregnancy tests weekly for the first month of treatment and then monthly until 1 month after stopping therapy. Females with irregular menses must have pregnancy tests every 2 weeks while receiving thalidomide therapy. Any positive qualitative pregnancy test must be followed by a quantitative pregnancy test.

Risk groups: *S.T.E.P.S.*® classifies patients into the following risk categories:
- female child not of childbearing potential
- female child of childbearing potential
- adult female not of childbearing potential
- adult female of childbearing potential
- adult male
- male child.

Authorise dispensing: Upon completion of a patient and/or prescriber survey resulting in no survey intervention, drug can be dispensed by a registered pharmacy.

Dispense: Pharmacy calls the IVR or customer service to dispense thalidomide to a patient.

Intervention: At-risk responses or inappropriate entries in the IVR system result in transfer of the caller to a Celgene *S.T.E.P.S.*® Intervention Specialist for intervention to evaluate and remedy at-risk behaviours when appropriate.

Fig. 1. Schematic of the procedures for prescription authorisation in the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.®) programme.

The rate of false positive pregnancy tests among females of childbearing potential was calculated for selected reporting period intervals. The numerator comprised the number of false positive pregnancy tests. The denominator comprised the number of pregnancy tests performed during the reporting period intervals. Two-sided 95% confidence intervals were calculated using the normal approximation. The Cochran-Armitage Chi-squared test was used to test for a linear association between time interval (2001, 2002, 2003, 2004) and the rate of false positive pregnancy tests.

Results

Since its approval in 1998 through to 31 December 2004, approximately 726 000 prescriptions for thalidomide were written. Approximately 124 000 patients (57% male and 43% female [table I]) were registered in the S.T.E.P.S.® programme. Approximately 6000 patients were females of childbearing potential, representing 5% of all patients and 11% of all female patients. The prescription of thalidomide in the US by reporting period interval is summarised in table I. The majority of the use of thalidomide (during the period 30 July 2001 to 31 December 2004) is for conditions other than erythema nodosum leprosum, the approved indication, with >88% used for the treatment of oncological conditions (table II).

The number of females of childbearing potential receiving thalidomide has increased since the approval of thalidomide (table I), with a corresponding increase in the number of pregnancy tests (table III). Since females of childbearing potential are required to have pregnancy tests before, during and after therapy, the number of tests is higher than the number of such patients enrolled in S.T.E.P.S.®. Quantitative β-hCG test results were provided for 64 cases, and 80% of these provided the laboratory reference value or ranges for the quantitative test (these data are available as supplementary material from http://www.adisonline.com/drs).

By 31 December 2004, 72 positive pregnancy tests have been reported in the S.T.E.P.S.® programme (69 were ultimately determined to be false positives): four cases in the first 3 years of marketing (September 1998–18 June 2001) and 68 cases from July 2001 to 31 December 2004 (table III). Thalidomide treatment was stopped immediately after a positive pregnancy test, and while test results were being evaluated. Three of the 72 cases represented true pregnancies (case 1, case 2 and case 3). In cases 2 and 3 the mechanism of S.T.E.P.S.® detected pregnancy prior to the patient receiving thalidomide.

Case 1 was a 44-year-old female with "high risk malignant melanoma" that had not responded to multiple prior therapies. She was unable to tolerate oral contraceptives and reported using two barrier methods of contraception. She had a negative pregnancy test on day 8 of her menstrual cycle before starting thalidomide, and had two subsequent negative pregnancy tests during the first month of treatment. On days 35 and 36 of thalidomide therapy she had positive qualitative serum β-hCG tests. Thalidomide therapy was stopped on day 35. On day 42 her quantitative β-hCG level was 1883 mIU/mL (reference value <5 mIU/mL for non-pregnant women). No further quantitative β-hCG results were reported. She had vaginal bleeding on day 63 and ultrasound examination "revealed only blood clots, so it was assumed that the patient passed the foetus" (wording verbatim from MedWatch form). No further follow-up was available.

Case 2 was a 26-year-old female with dermatomyositis who had a positive pregnancy test prior to receiving thalidomide. The patient did not receive thalidomide, but subsequently miscarried.

Case 3 was a 28-year-old female with malignant neoplasm of the vulva who had a positive pregnancy test prior to receiving thalidomide. The patient consulted with her physician and elected to undergo a termination and a tubal ligation. Subsequently, she began thalidomide therapy after it was confirmed that she was not pregnant.

The age range for patients with false-positive pregnancy tests was 12–56 years. These patients received thalidomide for treatment of multiple myeloma (54%), various neoplasms (39%) or other disorders (7%). The total duration of therapy for

Table I. Characteristics of patients receiving thalidomide (Thalomid®) in the S.T.E.P.S.® programme according to reporting period[a]

Risk classification group	Reporting period								Total[b]
	1998[c]	1999[c]	2000[c]	January–29 July 2001[c]	30 July–December 2001[d]	2002[d]	2003[d]	2004[d]	
Males [n (%)]	451 (57.7)	3633 (53.7)	6142 (54.9)	3889 (57.0)	10 555 (56.9)	14 590 (57.4)	15 483 (57.9)	15 889 (58.2)	70 632 (57.2)
Females not of childbearing potential [n (%)]	248 (31.7)	2617 (38.7)	4413 (39.4)	2614 (38.3)	7267 (39.2)	9603 (37.8)	10 009 (37.5)	10 155 (37.2)	46 926 (37.9)
Females of childbearing potential [n (%)]	83 (10.6)	514 (7.6)	633 (5.7)	323 (4.7)	739 (4.0)	1217 (4.8)	1237 (4.6)	1276 (4.7)	6022 (4.9)
Total[d][n (%)]	782 (100)	6764 (100)	11 188 (100)	6826 (100)	18 561 (100)	25 410 (100)	26 729 (100)	27 320 (100)	123 580 (100)
Thalidomide therapy									
Dose range (mg)	50–1050	50–1400	50–2400	50–2400	50–1400	50–1200	50–1200	50–1200	NA
Mean duration [d (SD)]	35.5 (19.8)	71.1 (66.2)	92.9 (82.5)	101.9 (86.5)	77.65 (444.6)	120.95 (100.4)	126.23 (101.4)	128.90 (102.9)	NA
Mean patient age									
All patients [y (SD)]	53.3 (NA)	57.4 (NA)	60.9 (NA)	62.4 (NA)	66 (14.1)	65 (14.4)	67 (14)	66 (14)	NA
Females of childbearing potential [y (SD)]	NA	NA	NA	NA	42 (9.3)	42 (9.0)	43 (9)	42 (9)	NA

a Represents data from a total of 726 032 prescriptions dispensed.

b Total of percentages may not equal 100% because of rounding.

c Data from Slone Epidemiology Center reports. Some patient demographic information was not available.

d Data from Celgene's S.T.E.P.S.® programme, modified on 30 July 2001. Because the S.T.E.P.S.® programme was modified 30 July 2001, data for the year 2001 is presented in this table for the period January–30 July 2001 and then separately for period 30 July 2001–December 2001.

NA = not available; **SD** = standard deviation; **S.T.E.P.S.®** = System for Thalidomide Education and Prescribing Safety.

Table II. Diagnoses of thalidomide (Thalomid®) recipients by risk classification group (30 July 2001–31 December 2004)[a]

Diagnosis (no. [%] patients)[b]	Males (n = 56 517 [57.66%])	Females not of childbearing potential (n = 37 034 [37.78%])	Females of childbearing potential (n = 4469 [4.56%])	Total (n = 98 020 [100%])
Oncological				
Multiple myeloma	25 988 (26.51)	20 618 (21.03)	1186 (1.21)	47 792 (48.76)
Renal cancer	4200 (4.28)	1567 (1.6)	194 (0.2)	5961 (6.08)
Myelodysplastic syndrome	5051 (5.15)	3145 (3.21)	85 (0.09)	8281 (8.45)
Brain cancer	1759 (1.79)	678 (0.69)	433 (0.44)	2870 (2.93)
Melanoma	2878 (2.94)	1141 (1.16)	466 (0.48)	4485 (4.58)
Prostate malignant neoplasm	3408 (3.48)	0	0	3408 (3.48)
Other neoplasms[c]	7071 (7.2)	5651 (5.77)	870 (0.89)	13 592 (13.87)
Dermatological				
Dermatological diseases	324 (0.33)	503 (0.51)	247 (0.25)	1074 (1.1)
Erythema nodosum leprosum	92 (0.09)	8 (0.01)	10 (0.01)	110 (0.11)
Haematological				
Haematological diseases	1686 (1.72)	1154 (1.18)	68 (0.07)	2908 (2.97)
Infectious diseases				
Infectious diseases	372 (0.38)	247 (0.25)	162 (0.17)	781 (0.8)
Gastrointestinal				
Digestive system/ genitourinary	326 (0.33)	148 (0.15)	105 (0.11)	579 (0.59)
Immunological				
Musculoskeletal/ rheumatological	212 (0.22)	347 (0.35)	230 (0.23)	789 (0.8)
Other	3050 (3.21)	1827 (1.86)	413 (0.42)	5390 (5.5)

a Data on diagnosis from October 1998 to July 2001 are not available.

b Total of percentages may not equal 100% because of rounding.

c Other neoplasms include colorectal, bladder/urethra, liver and other not specified neoplasms.

females of childbearing potential with false positive or indeterminate pregnancy test results ranged from <1 month to 34 months. The duration of treatment at the time of the first false positive pregnancy test in patients receiving thalidomide ranged from 4 days to 17 months. Fifteen of 69 patients had positive pregnancy tests that were determined to be false positive pregnancy tests before thalidomide therapy was initiated. For 68 of 69 patients, β-hCG levels were <350 mIU/mL. One patient with choriocarcinoma, a disease that is expected to produce high concentrations of β-hCG,[4] had levels >350 mIU/mL.

Discussion

The S.T.E.P.S.® programme is a risk management programme designed to prevent fetal exposures to thalidomide. S.T.E.P.S.® is an intensive, multi-component, integrated risk management programme that restricts drug use to registered clinicians, pharmacists and patients. Any suspected fetal exposure to thalidomide (either in female patients or female partners of male patients) in S.T.E.P.S.® participants must be reported immediately to the US FDA and Celgene.[5]

In accordance with the S.T.E.P.S.® programme, sexually active females of childbearing potential must use two appropriate methods of contraception simultaneously to prevent pregnancy for 4 weeks before, during and for 4 weeks following treatment with thalidomide. Appropriate methods of contraception include at least one highly effective method (e.g. intrauterine device, hormonal contraception,

Table III. Thalidomide (Thalomid®) prescriptions and pregnancy tests for females of childbearing potential

	1998–29 July 2001[a]	30 July–December 2001[b]	2002[b]	2003[b]	2004[b]
Prescriptions dispensed (n)	NA	2105	6517	7189	7978
Pregnancy tests (n)	NA	2195	6673	7822	8243
False-positive tests (n)[c]	5	6	20	68	82
Rate of false-positive tests[d] (95% CIs)	NA	0.27% (0.06, 0.49)	0.30% (0.17, 0.43)	0.87% (0.66, 1.08)	0.99% (0.78, 1.21)

a Data from Slone Epidemiology Center Reports.

b Data from Celgene's modified S.T.E.P.S.® programme effective from 30 July 2001.

c The number of false positive pregnancy tests is in excess of the number of cases of false positive pregnancy tests (n = 69) because some patients had more than one positive test result.

d False-positive pregnancy tests divided by number of pregnancy tests. The p-value from the Cochran-Armitage trend test was 0.7914 (Chi-squared [1 degree of freedom] = 0.0700), which indicates a non-significant relationship between year and the false-positive rate.

NA = not available; **S.T.E.P.S.®** = System for Thalidomide Education and Prescribing Safety.

tubal ligation or partner's vasectomy) and one additional effective method (e.g. latex condom, diaphragm or cervical cap). The aforementioned methods of pregnancy prevention must be used unless continuous complete abstinence from heterosexual sexual contact is the chosen method of pregnancy prevention. Females that may become pregnant and postmenarchal women who have not undergone a surgical menopause or who have not been postmenopausal naturally for at least 24 consecutive months (i.e. who have had menses at some time in the preceding 24 consecutive months) are considered to be females of childbearing potential in the S.T.E.P.S.® programme.

All patients agreed to comply with the methods of pregnancy prevention in S.T.E.P.S.®. Despite this, there have been infrequent reports regarding patient difficulties with complying with two forms of contraception. For female patients, one woman reported using two barrier methods, one woman reported that she had a tubal ligation and was not using another method and two women reported missing a dose of birth control pills. Ten male patients reported not using a condom.

According to S.T.E.P.S.®, females of childbearing potential must also have periodic pregnancy testing. Such patient must have a pregnancy test (sensitivity of at least 50 mIU/mL) performed within the 24 hours prior to beginning thalidomide therapy. Pregnancy testing should occur weekly during the first 4 weeks of use, then at 4-week intervals in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. Pregnancy testing should also be done if any female of childbearing potential misses her period or has any abnormality in menstrual bleeding. Any positive qualitative urine pregnancy test is followed by a more sensitive qualitative serum and/or a quantitative serum pregnancy test.

Thalidomide is present in the semen of male patients receiving the drug. Male patients receiving thalidomide who are sexually active with women who are or could become pregnant must always use a latex condom during any sexual contact, even if the male patient has undergone a successful vasecto-

my. However, the risk to the fetus from exposure to thalidomide in the semen is unknown. To date there have been 18 reports to the S.T.E.P.S.® programme of pregnancies in female partners of male patients taking thalidomide: 14 normal newborns, one ectopic pregnancy termination and three pregnancies with limited or no available follow-up information.

The initial design of the S.T.E.P.S.® programme retrospectively identified patient behaviours providing a risk of fetal exposure to thalidomide; therefore, procedural changes to the S.T.E.P.S.® programme were instituted in July 2001. These changes were designed to ensure that results from the required pregnancy tests were documented and linked to prescription activation and dispensing through an interactive voice response (IVR) system or via customer service prior to dispensing thalidomide. When an 'at risk' behaviour (e.g. a pending, outdated or positive pregnancy test result) is identified using the IVR system, the caller is transferred to a Celgene S.T.E.P.S.® Intervention Specialist.[3] On average, 5% of surveys require an intervention, verification or clarification of a patient or prescriber response prior to dispensing thalidomide.[3] The majority of all issues are addressed within 24 hours of identification by the IVR system. Thalidomide is not given if there is a known non-compliance issue.

Since the approval of Thalomid® in the US, only three women in the S.T.E.P.S.® programme have been identified as becoming pregnant: one after thalidomide was initiated and two at the time of enrolment but before the initiation of treatment with thalidomide. There were 69 other females of childbearing potential who had false-positive pregnancy tests after enrolling in S.T.E.P.S.® (please see http://www.adisonline.com/drs for individual patient information). Women who have false-positive β-hCG pregnancy tests usually have levels that remain consistently low,[6,7] as was seen in thalidomide users in this case series. Early pregnancy loss is associated with rapidly falling β-hCG levels;[8,9] therefore, the persistence of low β-hCG levels in the 69 cases is not suggestive of a true pregnancy that underwent early loss after exposure of the developing conceptus to thalidomide.

The frequency of false-positive pregnancy tests as a percentage of pregnancy tests performed (0.27–0.99%) has remained stable since the beginning of the modified S.T.E.P.S.® programme that was initiated in July 2001 (table III), and the observed rate of false-positive pregnancy tests is comparable to estimated rates of false-positive pregnancy tests in the general population of females of childbearing potential.[7] Pregnancy rates among comparable females not taking thalidomide were not available for comparison. The occurrence and general management of false-positive pregnancy tests are reviewed elsewhere.[10] Serial pregnancy tests, specialised laboratory tests, pelvic ultrasound or medical consultation can help distinguish between true- and false-positive pregnancy tests. In this series, nine cases had further clinical evaluation for positive pregnancy tests beyond repeat β-hCG testing: six had ultrasound studies, three had CT scans and one had further laboratory evaluation.

The institution of the IVR system in July 2001 was designed to identify patients exhibiting behaviours providing risk for fetal exposure and to remedy those behaviours prior to dispensing thalidomide. The continued ongoing evaluation of S.T.E.P.S.® will be essential to evaluate the programme's performance and to guide future refinements to the programme, in order for it to achieve its objectives.

Even with the use of thalidomide for a variety of medical conditions, the majority of which were for haematological malignancies (e.g. multiple myeloma) and solid organ tumours, the amount of thalidomide used in the US is relatively small. Similar risk management programmes for other drugs that have demonstrated adverse risks associated with fetal exposure, such as isotretinoin,[11] have been developed and implemented by drug manufacturers. The Celgene S.T.E.P.S.® programme has been licensed to several other drug manufacturers with the regulatory involvement of the FDA, for the increased surveillance and monitoring of physicians, pharmacists and patients, to prevent fetal ex-

posure to drugs. The vigilance of physicians, pharmacists, patients, Celgene and the FDA has contributed to the success of S.T.E.P.S.® in preventing pregnancy in females receiving thalidomide.

Conclusions

The S.T.E.P.S.® programme has been successful in preventing fetal exposure to thalidomide. Of the 6022 females of childbearing potential registered in the S.T.E.P.S.® programme, one patient became pregnant while receiving the drug and two additional patients were identified as pregnant and were not permitted to start thalidomide treatment. This 'real time' risk management programme may be a useful model to prevent exposure of pregnant women to other drugs that are known human teratogens or that are suspected to be teratogenic (based upon drug class or findings in experimental animal studies). Because important clinical decisions may be made on the basis of the results of pregnancy testing, clinicians using thalidomide must remain vigilant in evaluating every female with a positive pregnancy test until pregnancy is either confirmed or ruled out. Both the FDA and Celgene remain committed to preventing fetal exposure to thalidomide.

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