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Thalomid® (Thalidomide) Capsules

A Review of the First 18 Months of Spontaneous Postmarketing Adverse Event Surveillance, Including Off-Label Prescribing

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Abstract

The sedative/hypnotic thalidomide was withdrawn from the worldwide market nearly 40 years ago, because of its teratogenic and neurotoxic effects. Thalidomide was later found to very effectively suppress erythema nodosum leprosum (ENL). The US Food and Drug Administration (FDA) has approved Thalomid® (thalidomide) capsules for the acute treatment of the cutaneous manifestations of moderate to severe ENL. Thalidomide is currently under investigation for the treatment of a wide variety of diseases, including conditions thought to have an inflammatory or immune basis, malignancies and complications of infection with HIV. Interest in the potential anti-inflammatory, immunomodulatory and anti-

angiogenic effects of thalidomide has resulted in off-label use of prescription thalidomide.

During the first 18 months of spontaneous postmarketing adverse event surveillance for Thalomid®, 1210 spontaneous postmarketing adverse event reports were received for patients treated with prescription thalidomide for all therapeutic indications, including off-label use. The most common adverse events spontaneously reported would have been expected on the basis of the current Thalomid® labelling/product information.

The current labelling/product information reflects what was known about the risks associated with thalidomide therapy in limited patient populations at the time of the approval of Thalomid®. With the postmarketing use of thalidomide in populations other than patients with ENL, it becomes increasingly important to identify patient groups that may be particularly susceptible to specific adverse drug effects and to identify conditions under which specific adverse events may be more likely to occur. Oncology patients may represent a patient population with increased susceptibility to thalidomide-associated adverse effects, including thromboembolic events. Consideration of the spontaneous postmarketing safety surveillance data may help to identify and characterise factors associated with increased risk in this and other patient groups.

Serious unexpected adverse events reported with sufficient frequency to signal previously undetected product-event associations for which there may potentially be plausible evidence to suggest a causal relationship have included seizures and Stevens-Johnson syndrome. The potential effects of thalidomide on wound healing are also being closely monitored.

Premarketing human clinical trials of drug products are inherently limited in their ability to detect adverse events. Broader postmarketing experience with thalidomide in more varied patient populations and more experience in the setting of long term thalidomide use will increase our ability to detect rare adverse events and to identify signals that may need to be evaluated in more controlled settings.

Thalidomide (α-phthalimidoglutarimide) was marketed in the 1950s and early 1960s as an oral sedative/sleep aid in approximately 42 countries worldwide. Notable for its prompt onset of action and apparent safety, thalidomide gained rapid popularity among both physicians and patients as a purportedly safe alternative to barbiturates.[1] Concerns raised by emerging reports of the development of peripheral neuropathies in patients treated with thalidomide[2] were soon superseded by reports of an epidemic of congenital malformations associated with maternal thalidomide usage.[3,4] Thalidomide was withdrawn from the market worldwide by 1962, remaining available only for limited research purposes.

Sheskin,[5] in 1965, was the first to report that thalidomide suppresses erythema nodosum leprosum (ENL), a complication of the lepromatous form of Hansen's disease. Thalidomide has no direct action against *Mycobacterium leprae* but is believed to exert its effect in ENL through anti-inflammatory/immunomodulatory mechanisms.[6] Interest in the potential immunomodulatory and anti-inflammatory effects of thalidomide has led to new studies of the drug in other conditions thought to have an inflammatory or immune basis.

Thalidomide selectively inhibits tumour necrosis factor-α (TNFα) production by enhancing the degradation of TNFα messenger RNA.[7] In ENL patients, thalidomide has been shown to reduce serum levels of TNFα.[8] The effects of thalidomide on TNFα reported in the published literature appear to vary in different underlying disease states and also within the same diseases, depending on the

study methodology and duration of thalidomide therapy. Studies *in vitro* suggest that thalidomide can either enhance or suppress the synthesis of TNFα, depending on the type of cells stimulated.[9,10] In studies of the immunological and metabolic effects of thalidomide in HIV-seropositive patients, plasma levels of TNFα increased significantly with thalidomide treatment, despite positive clinical effects.[11,12] The data potentially suggest that thalidomide may exert a bidirectional, dose-dependent effect on TNFα production, depending on the target cell type and the mechanisms of cellular activation involved.

The anti-inflammatory and immunomodulatory properties of thalidomide may not be restricted to selective alterations in the regulation of TNFα production. Multiple immunomodulatory effects of thalidomide have been demonstrated *in vitro* and *in vivo*. Preincubation of normal human polymorphonuclear leucocytes with thalidomide caused a dose-independent inhibition of chemotaxis, but direct addition of the drug to the attractant serum failed to produce such inhibition.[13] Thalidomide also significantly decreased monocyte phagocytosis *in vitro* without apparent cytotoxicity[14] and inhibited proliferative T cell responses.[15] *In vivo*, thalidomide suppressed immunoglobulin M antibody production in a murine system[16] and decreased circulating immunoglobulin levels in patients with systemic lupus erythematosus.[17] Thalidomide, in human-equivalent doses, has been shown to suppress neutrophil infiltration in the carrageenin rat paw oedema model, resulting in an anti-inflammatory effect.[18] In healthy male volunteers, thalidomide produced a decrease in the circulating helper T cell to suppressor T cell ratio (CD4+ : CD8+) as a result of a highly significant decrease in CD4+ lymphocytes and an apparent increase in suppressor CD8+ lymphocytes.[19] In patients with ENL, thalidomide's effectiveness was consistently associated with a decrease in circulating CD4+ lymphocytes.[20] Thalidomide enhanced the synthesis of interleukin-2 (IL-2) in cultures of peripheral blood mononuclear cells from healthy donors and from HIV-infected patients.[21,22] Increased production of IL-2 by activated T cells has been suggested as a potential mechanism through which thalidomide may exert some of its immunomodulatory effects.[22]

Orally administered thalidomide has been shown in several animal models to be an inhibitor of angiogenesis induced by basic fibroblast growth factor (bFGF).[23,24] Because angiogenesis is a prerequisite for rapid tumour growth and metastasis,[25-29] thalidomide is currently under investigation as an inhibitor of angiogenesis in humans for the treatment of tumours that are not responsive to standard therapy.

The US Food and Drug Administration (FDA) approved the Thalomid® capsule formulation of thalidomide for US prescription market availability on 16 July 1998.

1. Thalomid® (Thalidomide) Pharmacokinetics and Metabolism

In addition to the studies from the current published literature, the pharmacokinetics of Thalomid® (thalidomide) capsules have been evaluated in 5 clinical studies in healthy male volunteers, Hansen's disease patients and HIV-seropositive patients. Intravenous pharmacokinetic studies have not been performed with thalidomide, because of its low solubility in acceptable solvents. Therefore, the absolute bioavailability, true elimination half-life, systemic clearance and volume of distribution of thalidomide have not been conclusively determined. The Thalomid® formulation of thalidomide has a pharmacokinetic profile best described by a 1-compartment model with first-order absorption and elimination.[30,31] At lower doses, the extent of Thalomid® absorption from the gastrointestinal tract is proportional to the dose. At doses in excess of 200mg, a plateauing of peak plasma concentration is observed with an associated delay in the time to peak concentration. The elimination half-life for higher Thalomid® doses becomes a function of absorption rate limitations, with the elimination rate being faster than the absorption rate.[30,32] The following is a summary of known pharmacokinetic data for thalidomide from all currently

available sources, including the unpublished clinical pharmacokinetic studies:[30-35] molecular weight = 258.23; peak serum concentrations after oral administration are reached at 3.2 ± 1.4 hours; volume of distribution = 84.1 ± 32.2L; absorption half-life = 1.03 ± 0.79 hours; elimination half-life = 6.17 ± 2.56 hours; total body clearance rate = 10.9 ± 1.7 L/h.

Thalidomide is a nonpolar lipophilic compound and is fairly insoluble (solubility in water = 0.06 mg/ml). In human blood, the geometric mean plasma protein binding was 55 and 66%, respectively, for (+)-(*R*)- and (–)-(*S*)-thalidomide.[36] The urinary excretion of thalidomide has been observed to be approximately 0.6 ± 0.22% of a total oral dose over 24 hours, suggesting a predominantly nonrenal route of excretion. After a single 200mg oral dose, thalidomide could be detected in plasma and urine up to 24 hours. Thalidomide was not detected in the urine beyond 48 hours. No thalidomide metabolites were detected in either plasma or urine after 24 hours.[32-34] Thalidomide pharmacokinetics do not to change with long term administration.[31,37]

The safety, efficacy and pharmacokinetics of thalidomide have not been specifically studied in patients with renal impairment. Existing data regarding thalidomide metabolism do not suggest that dosage adjustment should be necessary in patients with renal dysfunction.[34] It is not known whether thalidomide is dialysable. In a controlled clinical study of thalidomide in haemodialysis patients with uraemic pruritus, no adverse effects of thalidomide were reported.[38] Published case reports of thalidomide therapy in patients with chronic renal insufficiency who did not require dialysis have not suggested any untoward effects of thalidomide on renal function.[39] Thalidomide has, however, been commonly reported to cause hypotension.[32,35] Although thalidomide has no known direct action on the kidneys, it is theoretically possible that in marginally hydrated patients or patients at risk for renal dysfunction, the hypotensive effect of thalidomide could cause mild to moderate renal hypoperfusion, resulting in prerenal azotaemia. During therapy with thalidomide, careful monitoring of blood pressure and hydration and cautious use of concomitant nephrotoxic drugs and other drugs that may cause or exacerbate hypotension may be warranted in patients at risk for renal dysfunction.

The safety, efficacy and pharmacokinetics of thalidomide have not been specifically studied in patients with hepatic dysfunction. Thalidomide does not undergo significant hepatic enzyme-dependent metabolism.[32,40,41] In aqueous solution at physiological pH, thalidomide decomposes by spontaneous hydrolysis.[41] *In vitro* studies using a large range of human cloned cytochrome P450 (CYP) enzymes, rat liver homogenates and human liver homogenates have shown thalidomide to be a poor substrate for CYP-dependent mono-oxygenase reactions, with negligible thalidomide metabolism by CYP isozymes. Thalidomide also did not inhibit the metabolism of any CYP isozyme-specific substrates.[32,40]

Thalidomide is not known to have any drug-drug interactions, but specific drug-drug interactions have not been systematically studied with Thalomid®. Thalidomide has been reported to enhance the CNS depressant effects of barbiturates, alcohol, chlorpromazine and reserpine.[42,43] The sedative action of thalidomide is antagonised by methylphenidate and methamphetamine.[42] Steady-state plasma concentrations of thalidomide did not affect the single dose pharmacokinetics of orally administered hormonal contraceptives (ethinyl estradiol and norethindrone).[31]

2. Thalomid® Marketing Status

The US is currently the only country in which Thalomid® is approved for marketing. Thalomid® is indicated for acute treatment of the cutaneous manifestations of moderate to severe ENL and for maintenance therapy for the prevention and suppression of the cutaneous manifestations of ENL. Thalomid® is not indicated as monotherapy for such treatment in ENL in the presence of moderate to severe neuritis.

Because of the known teratogenic effects of thalidomide and in an effort to prevent, to the greatest extent possible, any chance of fetal exposure to thalidomide, Thalomid® is approved for marketing only under a special restricted distribution programme mandated by the FDA. Under this programme, the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.™), only prescribers and pharmacists registered with the programme are allowed to prescribe and dispense thalidomide.[44] In addition, patients must be advised of, agree to, and comply with the requirements of the S.T.E.P.S.™ programme. To monitor patient compliance with the S.T.E.P.S.™ programme, all patients must complete the S.T.E.P.S.™ programme informed consent and participate in a mandatory and confidential surveillance registry. Patient enrolment in the S.T.E.P.S.™ programme began on 1 October 1998.

Because Thalomid® is approved for marketing only under the restricted distribution system specified by the S.T.E.P.S.™ programme, it is possible to monitor the total number of male and female patients for whom thalidomide has been prescribed. During the first 18 months of market availability, 28 241 prescriptions (both new prescriptions and refills) were filled for 10 456 patients enrolled in the S.T.E.P.S.™ programme. Thalidomide was prescribed for 4776 female patients (approximately 46% of all patients enrolled in the S.T.E.P.S.™ programme). Approximately 16% of the female patients treated with prescription thalidomide were identified to be of childbearing potential.

The mean age of the patients for whom thalidomide was prescribed was 58 years (median age 59 years, range 3 to 95), the mean dose prescribed was 287 mg/day (range 50 to 1600 mg/day) and the mean duration of therapy was 8 weeks. Table I identifies the indications for thalidomide use, as reported by prescribers on the S.T.E.P.S.™ programme enrolment surveys. Although thalidomide is currently approved only for the treatment of ENL, interest in its potential anti-inflammatory, immunomodulatory and antiangiogenic effects has resulted in off-label use of Thalomid®. In particular, approximately 73% of Thalomid® use during the first 18 months of market availability has been in patients with malignancies.

3. Adverse Events

Premarketing human clinical trials of drug products are inherently limited in their ability to detect adverse events. Short trial duration, small trial size, narrow study populations and the limited set of therapeutic indications investigated particularly limit the capability of premarketing clinical trials to detect and define the frequency of all important adverse events. The broader population experience available in the postmarketing setting generally confers a greater ability to detect rare adverse events. The current Thalomid® labelling/product information reflects what is known about the risks associ-

Table I. Indications for Thalomid® (thalidomide) use as reported by prescribers on the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.™) programme enrolment surveys

Indication	No. of patients	% of patients
Autoimmune/immunological disease	621	6
Behçet's syndrome	101	1
Cancer	7633	73
brain	538	5
breast	198	2
gastrointestinal	627	6
genitourinary	941	9
haematological	326	3
lung	506	5
multiple myeloma	3557	34
skin	209	2
soft tissue	211	2
other	218	2
unspecified	302	3
Crohn's disease	146	1
Dermatological	239	2
Graft versus host disease	116	1
Hansen's disease/erythema nodosum leprosum	24	<1
HIV-related conditions	189	2
Other	641	6
Not reported/not interpretable	746	7
Total patients enrolled in the S.T.E.P.S.™ programme (1/10/1998 to 31/3/2000)	10 456	**100**

ated with thalidomide therapy from controlled clinical trials in ENL and HIV-related conditions, from uncontrolled investigational experience with thalidomide in patients with ENL and in patients who are HIV-seropositive and from additional events identified in the published literature or from spontaneous reports from other sources involving the investigational use of thalidomide in various other indications.[32,45] Because many of these reports were derived from uncontrolled clinical experience with thalidomide or from spontaneous reports from investigational populations of unknown size, accurate estimates of frequency cannot be made for the reported events, and a causal relationship between the occurrence of the events and therapy with thalidomide cannot be conclusively established.

During the first 18 months of spontaneous postmarketing adverse event surveillance for Thalomid,® 1210 spontaneous postmarketing adverse event reports were received for all therapeutic indications, including off-label use. There have been no reports of pregnancy in any female patients treated with Thalomid® capsules during this period. Dividing the number of spontaneous adverse event reports received by the number of patients known to be registered in the S.T.E.P.S.™ programme provides a crude spontaneous postmarketing adverse event reporting rate (CRR) of 11.6%.

The FDA defines a serious adverse event as any undesirable or unintended experience occurring at any drug dose that results in any of the following outcomes: death, a life-threatening event, inpatient hospitalisation or prolongation of existing hospitalisation, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, a life-threatening event, or inpatient hospitalisation may also be considered serious when, based on appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes included in the definition of a serious adverse event.[46] Applying the FDA criteria for seriousness, 493 (40.7%) of the spontaneous reports received during the first 18 months of postmarketing safety surveillance involved serious adverse events. It has been estimated that fewer than 1% of suspected serious adverse drug experiences are reported to the FDA.[47] Potentially, cases reported spontaneously to the Thalomid® postmarketing safety surveillance programme represent only a small portion of the number that have actually occurred, such that the crude spontaneous postmarketing adverse event reporting rate may underestimate the actual incidence of adverse events by up to 100-fold.

3.1 Common Spontaneously Reported Adverse Events

Table II identifies the most common postmarketing adverse events that have been spontaneously reported during the first 18 months of market availability of Thalomid®. All adverse events are identified using the preferred terms from the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART).[48]

3.1.1 Drowsiness/Sedation/Asthenia

The sedative effect of thalidomide may be experienced differently by individual patients. Signs and symptoms commonly attributed to the sedative action of thalidomide include dizziness, weakness/fatigue (COSTART: asthenia), hangover, muscle incoordination, unsteady gait, tremulousness, blurred vision, mood changes and confusion. Somnolence and asthenia were reported from clinical trials in

Table II. Most common postmarketing adverse events spontaneously reported for Thalomid® (thalidomide) capsules (1 October 1998 to 31 March 2000)

Adverse event	No. of patients	Crude spontaneous postmarketing reporting rate (%)
Somnolence	183	1.8
Rash	143	1.4
Asthenia	127	1.2
Peripheral oedema	110	1.1
Paraesthesia	91	0.87
Dizziness	87	0.83
Constipation	75	0.72
Dyspnoea	69	0.66
Leucopenia	52	0.5
Total patients enrolled	10 456	**100**

both patients with ENL and patients with HIV-related conditions. The incidence of somnolence and asthenia reported from clinical trials in patients with ENL (thalidomide 50 to 300 mg/day was 37.5% and 8.3%, respectively. From clinical trials among patients with HIV-related conditions, 36.1% of patients treated with thalidomide 100 mg/day and 37.5% of those treated with 200 mg/day reported somnolence. Corresponding reports for asthenia were ≈6 and 22%. The incidence of somnolence and asthenia in HIV-seropositive patients treated with placebo was 11.4 and 2.9%, respectively.[32,45] In a study evaluating the antitumour effect of thalidomide (200 to 800 mg/day) in refractory multiple myeloma, up to 43% of the patients reported somnolence and up to 48% reported weakness or fatigue.[49] The CRR is 1.8% (183 reports) for drowsiness/sedation (COSTART: somnolence) and 1.2% (127 reports) for weakness/fatigue (COSTART: asthenia).

The hypnosedative properties of thalidomide are believed to be due to activation of diencephalic (thalamic and hypothalamic) sleep centres and are dose related.[50,51] Unlike barbiturates, thalidomide does not depress CNS neuronal function via the enhancement of γ-amino butyric acid (GABA)-mediated neurotransmission.[50] Even at high doses, thalidomide does not cause anaesthesia or respiratory depression.[42] The sedative action of thalidomide is antagonised by methylphenidate and methamphetamine.[42] The use of methylphenidate or methamphetamine to counteract thalidomide-associated somnolence has not been evaluated in controlled clinical trials.

Administering thalidomide at bedtime minimises potentially deleterious effects due to excessive daytime somnolence, but patients should be cautioned to avoid situations in which drowsiness could be hazardous. For patients experiencing significant daytime somnolence, it may be necessary to re-evaluate their entire medication regimen and, if clinically appropriate, to consider adjusting the doses of other concomitant medications, including opioid analgesics, antidepressants, anxiolytics and other sedative/hypnotics that could cause or increase daytime somnolence.

3.1.2 Rash

Rash was reported from clinical trials of thalidomide in both patients with ENL and patients with HIV-related conditions. The incidence of rash reported from clinical trials in patients with ENL (thalidomide 50 to 300 mg/day) was 25%. From clinical trials among patients with HIV-related conditions, 41.6% of those treated with thalidomide 100 mg/day and 43.8% of those receiving 200 mg/day reported rash. The incidence of rash in HIV-seropositive patients treated with placebo was 37.1%.[32,45] In refractory multiple myeloma, rash was reported for up to 26% of the patients.[49] The CRR for rash is 1.4% (143 reports).

The incidence and severity of thalidomide-associated cutaneous reactions may vary depending on the patient's underlying disease state and immune status. The most common rash described in association with thalidomide use is a pruritic, erythematous, macular rash over the trunk, back and proximal extremities, which does not appear to be dosage related.[51] The development of rash has been most frequently reported 10 to 14 days after starting therapy with thalidomide.[51] The clinical experience with thalidomide in ENL described in the published literature suggests that few patients (<1%) developed a transient, thalidomide-associated allergic dermatitis that could generally be controlled with oral antihistamines and that did not require discontinuation of therapy. When thalidomide therapy was discontinued, the allergic dermatitis usually resolved within 24 hours. Some patients were successfully rechallenged with thalidomide at lower doses.[52]

Published reports suggest that the incidence of thalidomide-associated rash may be higher in patients with AIDS.[43,53] This increased incidence appeared to be associated with lower CD4+ T cell counts, and 25% of AIDS patients who developed a thalidomide-associated rash also had known hypersensitivity to cotrimoxazole (trimethoprim-sulfamethoxazole).[51] Severe thalidomide-associated hypersensitivity reactions have been reported in

HIV-seropositive patients. In some cases, rechallenge with thalidomide resulted in immediate, severe, sepsis-like hypersensitivity reactions with rash, fever, shaking chills, tachycardia and hypotension requiring prompt medical intervention.[51,54] There are currently no controlled data available regarding the incidence of rash in patients with malignancies treated with thalidomide.

Serious dermatological reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN), which may be fatal, have rarely been reported in association with thalidomide therapy.[55,56] Patients who develop rash during therapy with thalidomide should have prompt medical evaluation. If clinically appropriate, thalidomide therapy should be discontinued. If the rash is exfoliative, purpuric or bullous or if Stevens-Johnson syndrome or TEN is suspected, use of thalidomide should not be resumed.

3.1.3 Peripheral Oedema

Oedema was reported from clinical trials of thalidomide in both patients with ENL and patients with HIV-related conditions. The incidence of oedema reported from clinical trials in patients with ENL (thalidomide 50 to 300 mg/day) was 4.2%. From clinical trials among patients with HIV-related conditions, 8.3% of those treated with thalidomide 100 mg/day and 3.1% of those treated with 200 mg/day reported oedema. The incidence of oedema in HIV-seropositive patients treated with placebo was 2.9%.[32,45] In refractory multiple myeloma, oedema was reported for up to 22% of the patients.[49] The CRR for oedema is 1.1% (110 reports).

Peripheral oedema has been described as a frequent adverse effect of thalidomide in published reports of the investigational use of thalidomide for the treatment of patients with a variety of immunological, inflammatory and oncological conditions.[32,33,43,49,57-62] The mechanism by which thalidomide-associated oedema occurs is unknown. In most published reports, oedema associated with thalidomide therapy has been described as mild and short lived and responded to the temporary discontinuation of therapy until the swelling resolved. In some cases, diuretics were used successfully in conjunction with thalidomide therapy to control oedema.[59,61] The use of diuretics for the treatment of thalidomide-associated oedema has not been evaluated in controlled clinical studies.

As noted in the current Thalomid® product labelling/information, thalidomide has been reported in the published medical literature to slightly depress thyroid secretory activity.[33,42,43,45] Cases of hypothyroidism have been reported in association with thalidomide therapy.[63-65] The potential contribution of subclinical hypothyroidism to the adverse effects attributed directly to thalidomide is currently unknown. It may be prudent to perform thyroid function testing in patients with persistent symptoms or first onset of symptoms after prolonged therapy with thalidomide. Hypothyroidism may be a consideration in patients who experience late onset oedema, especially oedema of the pretibial region or peripheral oedema associated with periorbital puffiness.

3.1.4 Paraesthesia

Paraesthesias have been reported to be among the most common and most distressing symptoms of thalidomide-associated peripheral neuropathy.[66] Although neither paraesthesias nor peripheral neuropathy were reported from clinical trials of thalidomide in patients with ENL, in controlled clinical trials among patients with HIV-related conditions, 5.6% of those treated with thalidomide 100 mg/day and 15.6% of those receiving 200 mg/day reported paraesthesias. The incidence of paraesthesia in HIV-seropositive patients treated with placebo was 11.4%. Peripheral neuropathy was diagnosed in 8.3% of HIV-seropositive patients treated with thalidomide.[32,45] It is important to note that in advanced AIDS, up to 35% of patients not treated with thalidomide have been reported to have clinical evidence of neuropathy.[67,68] In refractory multiple myeloma, paraesthesias were reported for up to 28% of patients.[49]

The CRR for paraesthesia is 0.87% (91 reports). The diagnosis of peripheral neuropathy was confirmed in 39% of the patients for whom paraesthesias were reported. A pre-existing peripheral neu-

Table III. Characteristics of patients with Thalomid® (thalidomide)-associated paraesthesia

Patient characteristics	Patients with paraesthesias	All patients treated
Number of patients	91	10 456
Females (%)	52	46
Mean age (y)	61.5 (range 15-81)	58 (range 3-95)
Paraesthesia reported by a healthcare professional (%)	70	NA
Confirmed diagnosis of peripheral neuropathy (%)	39	Unknown
Diagnosis		
Cancer (%)	84.5	73
multiple myeloma (%)	44	34
Dermatological disease (%)	3.6	2
Autoimmune/Immunological disease (%)	3.6	6
Behçet's syndrome (%)	3.6	1
Crohn's disease (%)	2.4	1
HIV-related disease (%)	1.2	2
Other [Gorham's disease] (%)	1.2	6
History of pre-existing neuropathy (%)	26	Unknown
Pre-existing diabetes mellitus (%)	1.4	Unknown
Pre-existing thyroid disease (%)	8.2	Unknown
Treatment		
Mean duration of treatment to onset of paraesthesia (days)	32 (range 1-202)	NA
Mean daily dose (mg)	293 (range 50-900)	287 (range 50-1600)
Mean total cumulative dose (g)	11 (range 0.15-72)	Unknown
Treatment discontinued (%)	40	Unknown

NA = not applicable.

ropathy predating therapy with thalidomide had been diagnosed in 26% of these patients. The published literature suggests that the incidence of thalidomide-associated peripheral neuropathy is highest in women, elderly patients, immunosuppressed patients, patients with AIDS, patients with underlying malignancies, patients with concurrent underlying chronic illnesses, patients with diabetes mellitus or thyroid disease, and patients treated with higher total cumulative thalidomide doses.[66,69-72] Coadministration of thalidomide with alcohol or other medications known to cause peripheral neuropathy may increase the likelihood for the development of peripheral neuropathy.[72,73] Table III summarises the characteristics of patients for whom spontaneous postmarketing reports of paraesthesia have been received.

Thalidomide-associated peripheral neuropathy is a distal symmetric axonopathy, characterised by axonal degeneration without demyelination affecting mainly sensory fibres in the distal lower limbs with progression proximally (dying back phenomenon).[66,70,72,73] Although the pathogenic mechanism responsible for toxic polyneuropathy is not currently known, there is evidence to suggest that it may involve cytokine-mediated (TNFα, IL-1) inhibition of nerve growth factor.[74] Thalidomide-associated neuropathy manifests primarily with sensory signs and symptoms, especially in the distal lower limbs. Signs and symptoms may include symmetrical painful paraesthesias of the hands and feet, hyperaesthesia, pallor and coldness of the fingers and toes, and superficial sensory loss (increased thresholds to vibration, temperature, light touch and pin-prick sensations). In more advanced peripheral neuropathy, clinical signs and symptoms may progress to muscle cramps, muscle weakness (especially minor intrinsic foot weakness), postural tremor, decreased muscle stretch reflexes, palmar erythema and brittle nails.[66,73,75,76]

In patients with pre-existing neuropathies or those at increased risk for the development of peripheral neuropathy, consideration should be given to baseline evaluation and monitoring using electrophysiological nerve conduction studies and/or quantitative sensory testing devices.[57,70] The earliest finding, which may predate clinical symptoms, may be increased somatosensory evoked potential latency after sural nerve stimulation. Sensory nerve action potential amplitudes are decreased (sural, median and peroneal nerves).[69,75] There is relative conservation of conduction velocities.[66,69]

Although the correlation between the development of peripheral neuropathy and the cumulative dose of thalidomide is not clear, there is a suggestion of dose dependence, with the development of neuropathy after cumulative thalidomide doses of 40 to 50g.[57,77,78] Neuropathy has, however, been reported with cumulative thalidomide doses of only 3 to 6g, and individual susceptibility has been suggested to be more relevant to the development of neuropathy than dose or duration of thalidomide therapy.[69,78]

Sensory symptoms of peripheral neuropathy often improve after discontinuation of thalidomide therapy but may not resolve completely.[57,66,70,78] Electrophysiological abnormalities may persist despite resolution of symptoms.[57,66] Signs and symptoms of neuropathy may continue to progress or first appear 8 to 16 weeks after discontinuation of the drug (coasting phenomenon).[66,70,76] Continuation of therapy may result in progressive or permanent neuropathic changes.[70,77,78] If clinically appropriate, thalidomide therapy should be discontinued with the first signs or symptoms of neuropathy. Treatment with thalidomide should be reinitiated only if the neuropathy resolves completely. Patients who discontinue thalidomide with the earliest signs or symptoms of neuropathy are more likely to experience rapid and complete recovery.[57,66]

3.1.5 Dizziness/Hypotension/Bradycardia

Dizziness, hypotension, orthostatic hypotension and bradycardia have all been reported in association with thalidomide therapy. Dizziness was reported from clinical trials in both patients with ENL and patients with HIV-related conditions. The incidence of dizziness reported from clinical trials in patients with ENL (thalidomide 50 to 300 mg/day) was 4.2%. From clinical trials among patients with HIV-related conditions, 19.4% of those treated with thalidomide 100 mg/day and 18.7% treated with 200 mg/day reported dizziness.[32,45] In refractory multiple myeloma, dizziness was reported for up to 28% of patients.[49] The CRR for dizziness is 0.83% (87 reports). In most cases, it is not clear from the spontaneous reports whether dizziness was associated with hypotension or was a consequence of excessive sedation with normal blood pressure.

Hypotension and bradycardia have been reported from the uncontrolled investigational use of thalidomide in patients with ENL and in HIV-seropositive patients.[32,45] The CRR for hypotension and bradycardia are 0.32% (33 reports) and 0.12% (13 reports), respectively. The mechanism by which thalidomide produces dizziness, hypotension, orthostatic hypotension or bradycardia in humans has not been conclusively determined. In preclinical investigations in animal species, thalidomide in doses up to 125 mg/kg did not affect heart rate, blood pressure or respiration. No significant effects on the cardiovascular, respiratory or autonomic nervous systems could be elicited.[42] Some investigators have suggested that the occurrence of dizziness and hypotension may be related to the central sedative action of thalidomide.[43] In asymptomatic HIV-seropositive individuals, single oral 100 and 200mg doses of thalidomide consistently resulted in significant, dose-dependent decreases in supine systolic and diastolic blood pressure.[35] Peak decreases in blood pressure occurred between 1 and 2 hours after administration, followed by a recovery to baseline between 4 and 8 hours after administration. Decreases in blood pressure were not accompanied by reflex tachycardia, and the baroreceptor reflex after orthostatic changes remained intact. These observations suggest that the hypotensive effect of thalidomide probably did not involve any direct action on the peripheral vasculature but was most likely centrally mediated, possibly via activation of the vasovagal pathway.[35]

Administering thalidomide at bedtime potentially minimises symptoms due to decreases in blood pressure, but patients should be cautioned to avoid situations in which dizziness could be hazardous and to sit upright for several minutes before standing up from a recumbent position. For patients experiencing significant dizziness, hypotension and/or bradycardia, it may be necessary to re-evaluate their entire medication regimen and, if clinically appropriate, to consider adjusting the doses of other concomitant medications, including diuretics, vasodilators, phosphodiesterase type 5 (PDE5) inhibitors, antihypertensive agents, other cardiovascular medications or agents for prostatic hypertrophy (α-adrenergic blockers) that could contribute to or exacerbate dizziness, hypotension or bradycardia. Concurrent therapy with thalidomide and diuretics, vasodilators, PDE5 inhibitors, antihypertensive agents, α-adrenergic blockers and other cardiovascular medications has not been evaluated in controlled clinical trials.

Although thalidomide has no known direct action on the kidney, patients with impaired renal function or other underlying risk factors for renal dysfunction, hypotension or dehydration may be at increased risk for mild to moderate renal hypoperfusion resulting from the hypotensive effect of thalidomide. Careful monitoring of blood pressure and hydration and cautious use of concomitant nephrotoxic drugs and other drugs that may cause or exacerbate hypotension are probably warranted in at-risk patients treated with thalidomide. Because thalidomide may depress thyroid secretory activity,[33,42,43,45] hypothyroidism may be a consideration in patients with persistent symptoms or first onset of symptoms after prolonged therapy with thalidomide, particularly significant bradycardia.

3.1.6 Constipation

Constipation was reported from clinical trials of thalidomide in both patients with ENL and patients with HIV-related conditions. The incidence of constipation reported from clinical trials in patients with ENL (thalidomide 50 to 300 mg/day) was 4.2%. From clinical trials among patients with HIV-related conditions, 2.8% of those treated with thalidomide 100 mg/day and 9.4% treated with 200 mg/day reported constipation. Constipation was not reported by patients who were HIV-seropositive treated with placebo.[32,45] In refractory multiple myeloma, constipation was reported by up to 59% of patients.[49] The CRR for constipation is 0.72% (75 reports).

Although the mechanism by which thalidomide causes constipation is not currently known, it is suspected to involve neuromuscular colonic inertia with hypotonia.[42] Management of thalidomide-associated constipation has generally consisted of the use of mild laxatives, especially emollient or lubricant laxatives.[11,59] Constipation was also relieved by temporarily discontinuing therapy with thalidomide for 1 to 2 days.[59] Patients who can tolerate them may also benefit from mild stimulant laxatives. In adequately hydrated patients with normal renal function, saline or hyperosmotic laxatives may be tried. In severe cases, treatment as for acute, nontoxic megacolon with bowel evacuants and/or gastrointestinal prokinetic agents may need to be considered. In appropriate patients, consideration may be given to initiating a bowel regimen with a mild laxative at the start of thalidomide therapy, in an effort to prevent constipation. Concurrent therapy with thalidomide and laxatives, bowel evacuants or gastrointestinal prokinetic agents has not been evaluated in controlled clinical studies. Because thalidomide may depress thyroid secretory activity,[33,42,43,45] hypothyroidism may be a consideration in patients with persistent symptoms or first onset of symptoms after prolonged therapy with thalidomide, particularly severe or refractory constipation.

3.1.7 Dyspnoea

Although dyspnoea has previously been reported in association with thalidomide therapy, the frequency of spontaneous postmarketing reports has been somewhat unexpected. Dyspnoea was not reported from clinical trials of thalidomide in ENL or HIV-related conditions. Previously reported cases of dyspnoea had been identified from events reported in the published literature or from spon-

taneous reports from other sources involving the uncontrolled investigational use of thalidomide in various other indications.[32,45] The CRR for dyspnoea is 0.66% (69 reports).

The pathogenic mechanism or mechanisms underlying dyspnoea occurring during therapy with thalidomide are not currently known. 61 of the spontaneous postmarketing cases of dyspnoea (88%) were reported for patients treated with thalidomide for malignancies. 15 of these patients (25%) had pulmonary malignancies. Reports of 15 cases of mild 'shortness of breath' were received directly from consumers. In these cases, the patients had not been evaluated by healthcare professionals, and no aetiologies for the dyspnoea were identified. In 26 of the reported cases (38%), the treating physicians identified specific aetiologies for the patients' dyspnoea and assessed the reported events as not having been related to treatment with thalidomide. The aetiologies that were identified included anaemia, decompensation of pre-existing congestive heart failure, decompensation of pre-existing chronic obstructive pulmonary disease, pre-existing cardiac ischaemia, multiple myeloma with pre-existing cardiac and pulmonary amyloidosis, progressive malignancies with pre-existing pulmonary and/or pleural involvement, malignant pleural effusion, viral respiratory tract infection, pneumonia, allergic bronchopulmonary aspergillosis, asthmatic bronchitis, pulmonary vasculitis, acute respiratory distress syndrome, sepsis, anxiety, and docetaxel-related toxicity. Two patients had hypersensitivity reactions to thalidomide associated with dyspnoea, fever, rash, hypotension, and/or facial and laryngeal oedema.

13 of the patients for whom dyspnoea was spontaneously reported (19%) had radiographic examinations of the chest. In 12 of the 13 cases the radiographic evaluations supported specific aetiologies for the patients' dyspnoea. Eight patients had cardiac evaluations including electrocardiograms, echocardiograms, cardiac stress tests, gated blood pool imaging (MUGA), Holter monitoring and/or cardiac enzyme evaluations. In three cases, cardiac evaluations supported specific aetiologies for the patients' dyspnoea. The remaining 5 patients had normal cardiac evaluations.

Identification of a specific cause for dyspnoea is complicated by the multivariable pathophysiology and the variety of CNS, peripheral nervous system, lung and chest wall receptors believed to contribute to the subjective sensation of breathlessness. Diagnosis of the dyspnoeic patient is often difficult owing to similar presentations of different pathological processes and to the potential contributions of other concurrent diseases. Asthma, chronic obstructive pulmonary disease, pneumonia, congestive heart failure, cardiac ischaemia, interstitial lung disease and psychogenic dyspnoea account for approximately 85% of all cases of shortness of breath.[79]

Dyspnoea may be a prominent feature of the acute, subacute and chronic forms of drug-induced pulmonary disease.[80] Aside from hypersensitivity syndromes, interstitial pneumonitis with or without fibrosis is the most common pattern of injury described with drug-induced pulmonary disease. Direct cytotoxic effects of drugs or their metabolites on the respiratory epithelium, endothelium or interstitium evoke an inflammatory response leading to interstitial pneumonitis and, if persistent, to fibrosis.[80] None of the 13 patients who had radiographic examinations of the chest was reported to have had radiographic findings suggestive of interstitial lung disease.

Oedema has been described as a frequent adverse effect of thalidomide from controlled clinical trials and in published reports of uncontrolled investigational experience with thalidomide.[32,33,43,45,49,57-62] The mechanism by which thalidomide-associated oedema occurs is unknown. Pulmonary oedema has been reported from uncontrolled clinical experience with the investigational use of thalidomide in HIV-seropositive patients.[32,45] Because these reports came from uncontrolled clinical experience, a true incidence rate for pulmonary oedema cannot be determined, and a causal relationship between the occurrence of pulmonary oedema and therapy with thalidomide cannot be conclusively established. Generalised fluid retention with mild pulmonary con-

gestion may be a consideration in patients experiencing dyspnoea during therapy with thalidomide. To date, however, no objective evidence of pulmonary oedema has been reported for patients experiencing thalidomide-associated dyspnoea in the absence of known cardiovascular disease. From among the patients for whom spontaneous postmarketing reports of dyspnoea have been received, 21 (30%) also reported peripheral oedema.

Generalised weakness and fatigue have been among the most common spontaneously reported adverse events during thalidomide therapy (CRR 1.2%). 18 of the patients for whom dyspnoea was reported (26%) also experienced generalised weakness or fatigue. In some patients, the sensations of muscle weakness and fatigue may contribute to respiratory discomfort, resulting in excessive ventilation out of proportion to the patient's level of activity.[81-84] The sensation of dyspnoea is an inherently complex experience involving the processing of sensory information, as well as the subjective interpretation of these sensations.[82,83] The subjective nature of the awareness of the desire for increased breathing in the dyspnoeic patient underscores the possible role of affective or cognitive factors in the sensation of breathlessness and suggests the importance of cortical influences in the pathogenesis of dyspnoea. It is possible that for some patients the sensation of shortness of breath may be a component of the experience of the sedative/hypnotic effect of thalidomide.

3.1.8 Leucopenia

Neutropenia (COSTART: leucopenia) was reported from controlled clinical trials of thalidomide in patients with HIV-related conditions. The incidence of neutropenia in these trials was 16.7% in patients treated with thalidomide 100 mg/day and 25% in those treated with 200 mg/day. The incidence of neutropenia in HIV-seropositive patients treated with placebo was 8.6%. Neutropenia has also been reported from the investigational use of thalidomide in patients with ENL.[32,45] In refractory multiple myeloma, neutropenia was reported for <5% of patients at any dose level (200 to 800 mg/day).[49]

The CRR for neutropenia is 0.5% (52 reports). 49 of the spontaneous postmarketing cases of neutropenia (94%) occurred in patients treated with thalidomide for malignancies. More than 49% of the oncology patients for whom neutropenia was reported were receiving concomitant antineoplastic chemotherapy, and 28% had histories of neutropenia predating therapy with thalidomide. There are currently no controlled data available regarding the incidence of neutropenia in patients with malignancies treated with thalidomide. Table IV summarises the characteristics of patients for whom spontaneous postmarketing reports of neutropenia have been received.

Reports from the published literature suggest that HIV-seropositive patients may be at higher risk for the development of thalidomide-associated neutropenia.[43,51,85] Neutropenia has been reported to occur in approximately 8% of asymptomatic HIV-seropositive patients not treated with thalidomide. In advanced AIDS, approximately 75% of patients not treated with thalidomide develop neutropenia.[86,87]

The current FDA-approved precautions regarding thalidomide-associated neutropenia recommend that therapy should not be started in patients with absolute neutrophil counts (ANC) <750 cells/mm^3. The white blood cell count and differential should be monitored on an ongoing basis, especially in patients who may be at greater risk for the development of neutropenia. During therapy with thalidomide, if the ANC decreases to <750 cells/mm^3, the patient's entire medication regimen should be re-evaluated and, if the neutropenia persists, consideration should be given to withholding thalidomide, if clinically appropriate.[45]

3.2 Thromboembolic Events

Thromboembolic adverse events have previously been reported in association with thalidomide therapy.[32,45] The risk for the occurrence of such events in populations other than patients with ENL is not currently known. Evaluation of the frequency of thromboembolic events is particularly complex in patient populations that may have a relatively higher

Table IV. Characteristics of patients with Thalomid® (thalidomide)-associated neutropenia

Patient characteristics	Patients with neutropenia	All patients treated
Number of patients	52	10 456
Females (%)	54	46
Mean age (y)	56.4 (range 29-81)	58 (range 3-95)
Diagnosis		
Cancer (%)	94	73
multiple myeloma (%)	49	34
Dermatological condition (%)	2	2
HIV-related condition (%)	2	2
Other [neurofibromatosis] (%)	2	6
Treatment		
Mean duration of treatment to onset of neutropenia (days)	62 (range 5-330)	NA
Mean daily dose (mg)	421 (range 50-1600)	287 (range 50-1600)
Treatment discontinued (%)	42	NA
Therapy with thalidomide restarted (%)	39	NA
Event occurred after discontinuation of therapy with thalidomide (%)	2	NA
History of neutropenia predating therapy with thalidomide (%)	28	Unknown
Concomitant antineoplastic chemotherapy (%)	49	Unknown

NA = not applicable.

background frequency of thromboembolic events than is observed in patients with ENL. With the use of prescription thalidomide in patient populations that may be particularly susceptible to thromboembolic phenomena, consideration of the spontaneous postmarketing safety surveillance data may help to identify patient groups and other factors associated with increased risk. In particular, patients with malignancies may represent such a population with increased susceptibility to thromboembolic events. There are currently no controlled data regarding the incidence of such events in patients with malignancies treated with thalidomide. In a phase II trial of thalidomide administered as a daily 1200mg dose in 32 patients with recurrent high-grade astrocytomas and mixed gliomas, deep vein thrombosis was reported in 1 patient (3%). This event was not reported as having been clearly related to treatment with thalidomide.[88]

Adverse events reported from uncontrolled clinical experience with thalidomide in patients with ENL and in HIV-seropositive patients have included thrombophlebitis, thrombosis and pulmonary embolus.[32,45] During the first 18 months of US market availability, 27 spontaneous postmarketing reports of thromboembolic events were received for patients treated with prescription thalidomide (CRR 0.26%). 26 of the 27 reports were received for patients who were being treated for malignancies (CRR 0.34% for oncology patients). 12 of the patients were treated for multiple myeloma (44%). Other malignancies for which reports of thromboembolic events have been received include brain tumours (4 reports, 15%), lung cancer (3 reports, 11%), renal cell carcinoma (2 reports, 7%), unspecified malignancies (2 reports, 7%) and 1 report each for breast cancer, oesophageal cancer and nasopharyngeal cancer. Table V summarises the characteristics of patients for whom spontaneous postmarketing reports of thromboembolic events have been received.

Patients with cancer are predisposed to a hypercoagulable state associated with an increased risk for venous thromboembolism.[89-92] The published literature suggests that the overall reported clinical incidence of thromboembolic phenomena in oncology patients is approximately 15%.[90-93] However, incidences reported from autopsy series have been considerably higher.[93-95] Complications of alterations in haemostasis have been reported to repre-

sent the second most common cause of mortality in patients with cancer.[94] The risk of thrombosis in these patients varies with the type of underlying malignancy. Patients with mucin-secreting adenocarcinomas of the gastrointestinal tract, pancreatic cancer, ovarian cancer, lung cancer, acute promyelocytic leukaemia, myeloproliferative disorders and brain tumours have all been reported to be at increased risk for thromboembolic complications.[93] A variety of coagulation defects have been reported for patients with dysproteinaemias such as plasma cell myeloma or macroglobulinaemia.[96-98] The reported incidence of venous thromboembolism in patients with myeloproliferative disorders ranges from 3.6 to 11.53%.[91] There is also a much higher risk of venous and arterial thrombosis in patients with cancer during antineoplastic chemotherapy.[99]

The cause of thrombosis in patients with cancer is currently unknown but is probably multifactorial. The pathogenesis of the hypercoagulable state associated with malignancies may involve tumour cell interactions with pre-existing (acquired or hereditary) coagulation factors, the generation of procoagulant factors and the activation of platelets and/or vascular endothelium.[100-102] What effects, if any, thalidomide may have on normal coagula-

Table V. Characteristics of patients with Thalomid® (thalidomide)-associated thromboembolic events

Patient characteristics	Patients with thromboembolic events	All patients treated
Number of patients	27	10 456
Females (%)	43	46
Mean age (y)	61.7 (range 42-81)	58 (range 3-95)
Diagnosis		
Cancer (%)	96	73
multiple myeloma (%)	44	34
Behçet's syndrome (%)	4	1
Thromboembolic event		
Deep vein thrombosis (%)	67	NA
Deep vein thrombosis and pulmonary embolism (%)	33	NA
Treatment		
Mean duration of treatment to onset of event (days)	50 (range 5-118)	NA
Mean daily dose (mg)	356 (range 100-800)	287 (range 50-1600)
Treatment discontinued (%)	52	NA
Therapy with thalidomide restarted (%)	14	NA
Event occurred after discontinuation of therapy with thalidomide (%)	15	NA
Past history of thromboembolic events (%)	11	Unknown
Relevant concomitant medications		
Antineoplastic chemotherapy (%)	26	Unknown
Corticosteroids (%)	52	Unknown
Megestrol acetate (%)	4	Unknown
Conjugated estrogens (%)	4	Unknown
Other risk factors		
Knee surgery (no. of pts)	1	Unknown
Lower extremity trauma – soft tissue (no. of pts)	1	Unknown
Pathological fracture – femur (no. of pts)	1	Unknown
Total hip replacement surgery (no. of pts)	1	Unknown
Lower extremity varicose veins (no. of pts)	1	Unknown
Thrombocytosis (no. of pts)	1	Unknown

NA = not applicable; **pts** = patients.

tion factors, platelets or vascular endothelium, or the procoagulant activity of malignant cells are currently unknown. Because of presumed underreporting, the currently available uncontrolled data may not accurately reflect the risk for thromboembolic events in oncology patients treated with thalidomide. A number of controlled clinical trials are currently in progress to investigate the effects of thalidomide on the coagulation system in non-anticoagulated patients with multiple myeloma. In the absence of controlled data, it would be premature to recommend a prophylactic anticoagulant regimen during thalidomide therapy.

Although not formally studied, there is no known thalidomide-warfarin drug interaction. Uncontrolled clinical experience to date suggests that many patients who develop thromboembolic complications are able to continue thalidomide after the initiation of appropriate anticoagulation therapy. From among the total of 1210 patients for whom spontaneous postmarketing adverse drug experiences have been reported during Thalomid® therapy, 139 (13%) were known to have received concomitant therapy with warfarin. To date, 1 case (0.7%) of an excessively elevated international normalised prothrombin time ratio (INR) has been spontaneously reported. As with any patient treated with warfarin, during concomitant therapy with thalidomide, the patient's INR should be monitored closely until stable. Frequent periodic monitoring should continue after a stable anticoagulant regimen has been established.

Because thrombocytopenia has been reported in association with thalidomide therapy,[32,45] patients should have platelet counts checked within 3 to 5 days after starting concomitant anticoagulant therapy. Platelet counts should be monitored frequently until stable.

3.3 Serious Unexpected Adverse Events

During the first 18 months of US market availability of prescription thalidomide, 525 spontaneous postmarketing reports were received involving unexpected adverse events not currently described in the Thalomid® labelling/product information (43% of all spontaneous postmarketing reports). Applying the FDA criteria for seriousness, 369 of these reports (70%) involved serious unexpected events. In 280 of the serious unexpected adverse event reports (53%), patients were reported to have died because of progression of pre-existing malignancies. Although death due to underlying disease progression could be considered to be a lack of therapeutic effect, all of the patients who died were treated for therapeutic indications which are not yet approved indications for thalidomide. In a number of cases, it also appears that patients who were preterminal were started on thalidomide as palliative therapy, and the patients' deaths were not unexpected. Reports of nonfatal progression of patients' underlying diseases, other than ENL, accounted for 7.5% (28 reports) of the serious unexpected adverse event reports.

Although the requirement for registration in the S.T.E.P.S.™ programme provides a means to monitor the size of the population for which thalidomide is being prescribed, it is unusual to be able to establish with certainty through postmarketing surveillance that a causal relationship exists between exposure to a drug and a specific adverse event.[103] It has been suggested that for rare adverse drug experiences, coincidental drug-event associations are so unlikely that they warrant little concern. However, more than 3 spontaneous reports of an event are potentially considered to constitute a signal requiring further evaluation.[104] From among the serious unexpected adverse events spontaneously reported for Thalomid®, at least 3 reports have been received for each of the following events between 1 October 1998 and 31 March 2000: convulsion (18 reports), respiratory failure (15), pleural effusion (13), stupor (6), hypoxia (5), hallucinations (5), shock (4), hepatic failure (4), pneumothorax (4), coma (3), cerebral haemorrhage (3), Stevens-Johnson syndrome (3), skin ulcer (3) and paranoid reaction (3).

The decision to investigate a spontaneously reported event in a more controlled investigational setting must typically be based on the seriousness of the event, the plausibility of a causal relationship in the light of the drug's pharmacology, and the

strength of the evidence for a causal relationship, such as a positive rechallenge. All of the patients for whom respiratory failure, pleural effusion, hypoxia, shock, pneumothorax and cerebral haemorrhage were reported experienced progression of their underlying diseases during therapy with thalidomide. All but 3 of these patients were treated with thalidomide for very advanced refractory malignancies. The serious unexpected events reported for these patients were felt to have been complications of or the direct consequences of complications of their underlying malignancies, and the treating physicians assessed the events to have been unrelated to therapy with thalidomide.

One of the patients treated with thalidomide for an indication other than malignancy, who experienced serious unexpected adverse events, was a 65-year-old woman with sarcoidosis refractory to corticosteroid therapy. The patient also had concurrent diabetes mellitus. Before starting therapy with thalidomide, she had severe pulmonary fibrosis with respiratory insufficiency requiring mechanical ventilation. After 2 weeks of therapy with thalidomide 400 mg/day, the patient was successfully weaned from mechanical ventilatory support. She remained stable for approximately 2 months, before she experienced an acute exacerbation of her pulmonary disease with respiratory failure. The treating physician assessed the patient's events to have been unrelated to therapy with thalidomide.

A 59-year-old male patient with corticosteroid-refractory sarcoidosis with severe pulmonary fibrosis and bullous transformation was treated with thalidomide 400 mg/day for 16 days. During therapy, the patient experienced progressive pulmonary disease with respiratory failure requiring mechanical ventilation. The patient developed numerous complications including a pneumothorax. He died as a result of progressive respiratory compromise. The treating physician assessed the events and the patient's death to have been unrelated to therapy with thalidomide.

A third patient, a 59-year-old man with diabetes mellitus, was treated for pyoderma gangrenosum. After 10 days of therapy with thalidomide 400 mg/day, the patient was hospitalised with Gram-negative bacteraemia. He developed septic shock and died 4 days after therapy with thalidomide had been discontinued. The cause of death reported at autopsy was multiorgan system failure secondary to Gram-negative sepsis with septic shock, which the treating physician assessed to have been unrelated to therapy with thalidomide.

3.3.1 Seizures

Seizures (COSTART: convulsion) are not currently included among the events reported in the Thalomid® labelling/product information. During the first 18 months of US market availability, 18 spontaneous reports of seizures were received for patients (8 females and 10 males) treated with prescription thalidomide (CRR 0.17%). The mean age of the patients for whom seizures were reported was 51 (range 11 to 78) years. 11 patients (61%) had known pre-existing CNS disease or a past history of seizures. Eight patients (44%) had pre-existing hypertension, and 5 patients (28%), all of whom were treated for multiple myeloma, had pre-existing renal insufficiency or renal failure. Four patients were dialysis-dependent. Table VI summarises the characteristics of patients for whom spontaneous postmarketing reports of seizures have been received.

In 4 cases, the patients first developed seizure activity after therapy with thalidomide had been discontinued. Four patients continued therapy with thalidomide with no subsequent seizures reported. 14 patients discontinued therapy. Among these, 7 patients have had no subsequent seizures reported, 2 had subsequent seizures off thalidomide and 2 re-initiated thalidomide therapy with no subsequent reports of seizures.

13 of the 17 patients for whom complete information is available experienced the new onset of seizures during or after therapy with thalidomide. To date, the CRR for new onset of seizures during therapy with thalidomide has been approximately 0.12%. This rate is higher than the incidence of new onset of seizure disorders in adults, which is reported to occur annually in 0.03 to 0.05% of the general population.[105]

Table VI. Characteristics of patients with Thalomid® (thalidomide)-associated seizures

Patient characteristics	Patients with seizures	All patients treated
Number of patients	18	10 456
Females (%; no.)	44 (8)	46
Mean age (y)	50.8 (range 11-78)	58 (range 3-95)
Diagnosis		
Cancer (%; no.)	83 (15)	73
multiple myeloma (%; no.)	56 (10)	34
primary brain tumours (%; no.)	17 (3)	5
gastrointestinal (%; no.)	6 (1)	6
lung (%; no.)	6 (1)	5
brain metastases (%; no.)	6 (1)	Unknown
Graft versus host disease (%; no.)	11 (2)	1
Dermatological conditions (%; no.)	6 (1)	2
Past history of seizures predating therapy with thalidomide (%; no.)	22 (4)	Unknown
Treatment		
Mean duration of treatment to onset of event (days)	56 (range 6-211)	NA
Mean daily dose (mg)	371 (range 50-1000)	287 (range 50-1600)
Mean total cumulative thalidomide dose (g)	24	NA
Treatment discontinued (%; no.)	78 (14)	NA
Therapy with thalidomide restarted (%; no.)	14 (2/14)	NA
Event occurred after discontinuation of therapy with thalidomide (%; no.)	22 (4)	NA
Subsequent seizures reported after discontinuation of thalidomide (%; no.)	14 (2/14)	NA
Concurrent medical conditions		
CNS trauma (%; no.)	11 (2)	Unknown
CNS infection (%; no.)	17 (3)	Unknown
CNS surgery (%; no.)	17 (3)	Unknown
Renal insufficiency (%; no.)	28 (5)	Unknown
Chronic dialysis-dependent renal failure (%; no.)	22 (4)	Unknown
Hypertension (%; no.)	44 (8)	Unknown
Other suspect drugs (%; no.)	17 (3)	NA

NA = not applicable.

17 of the 18 patients for whom reports of seizure were received (94%) were treated with thalidomide for oncology-related indications. Overall, 74% of patients registered in the S.T.E.P.S.™ programme have been treated for oncology-related indications. The CRR for seizures in oncology patients treated with thalidomide is 0.2%. Ten of the 18 patients for whom seizures were reported (56%) were treated with thalidomide for multiple myeloma. Overall, 34% of patients registered to date in the S.T.E.P.S.™ programme have been treated for multiple myeloma. The CRR for seizures in multiple myeloma patients treated with thalidomide is 0.28%.

Oncology patients and patients with chronic renal failure may represent populations at increased risk for seizures. Neurological emergencies are common among cancer patients. In 1 study, neurological symptoms and signs were present in 38% of oncology-related emergency department visits.[106] Neurological emergencies may result from a direct effect of the malignancy, as a complication of metabolic abnormalities or the dysfunction of other organ systems, or as a sequela of therapy. Seizures are a presenting symptom in approximately 20 to 30% of patients with brain tumours.[107,108] Other causes of seizures in oncology patients in descending order of frequency include metastatic disease, treatment sequelae, primary CNS infection, cerebrovascular disease and metabolic abnormalities.[109] Metabolic abnormalities, especially

hypoglycaemia, hyperglycaemia, hyponatraemia, hypocalcaemia and hypercalcaemia account for 9% of acutely triggered seizures.[110] Patients with multiple myeloma and especially myeloma patients with renal insufficiency may be particularly at risk for such metabolic derangements. Approximately 35% of patients diagnosed with multiple myeloma are found at presentation to have renal impairment ranging from renal insufficiency with increased BUN and/or creatinine[111,112] to acute renal failure.[113-115] Up to 50% of multiple myeloma patients have minimal histological renal damage with apparently normal renal function.[113-116] Patients with renal failure have seizures related to several syndromes.[117] The incidence of seizures in dialysis patients not treated with thalidomide has been reported to be 4 to 8% per year.[118-121] Although specific metabolic abnormalities were not documented in all of the patients without known pre-existing CNS disease, such urgently treatable causes should be considered in any patient with seizures, if the clinical setting is appropriate.

One previous case of seizure activity during therapy with thalidomide for multiple myeloma was presented in an abstract at the 1999 meeting of the American Society of Hematology.[122] This case involved a 48-year-old man with multiple myeloma and renal failure who developed seizures and white matter changes on magnetic resonance imaging (MRI) scan after 8 months of therapy with thalidomide. He required haemodialysis for worsening renal failure due to light chain nephropathy, demonstrated on renal biopsy. After his second dialysis, the patient developed sudden onset of headaches, photophobia, nausea and vomiting and had 3 generalised tonic-clonic seizures. He was diagnosed with a subarachnoid haemorrhage. A search of the published literature failed to identify any other reports of seizures in humans treated with thalidomide for any indication. Thalidomide has been tested for anticonvulsant activity in a variety of animal species.[42] In rats, thalidomide had no anticonvulsant activity, when evaluated using a maximal electroshock procedure.[123] Thalidomide doses of 100 mg/kg did, however, reduce the median effective anticonvulsant doses (ED_{50}) of diphenylhydantoin and phenobarbital (phenobarbitone) in mice by ratios of 1.95 and 2.2, respectively. This potentiation of the anticonvulsant effects did not involve inhibition of the metabolic pathways of the anticonvulsant drugs in the liver and occurred without an increase in serum drug concentrations.[123]

One report from the published preclinical literature compared the ability of thalidomide and pentobarbital (pentobarbitone) to suppress the susceptibility to audiogenic seizures of rats withdrawn from sodium barbital.[124] Sodium barbital withdrawal seizures were compared in a placebo control group of rats, a sodium barbital-maintained group (500 mg/kg/day), a 50 mg/kg pentobarbital substituted group, a 30 mg/kg thalidomide substituted group, and a 60 mg/kg thalidomide substituted group (n = 6 for each group). Total scores of seizure activity obtained for each of the treatment groups during 6 scoring sessions were compared. The total scores obtained by rats maintained on sodium barbital and rats with substituted pentobarbital were markedly and significantly less than the total scores obtained by rats of the control withdrawn and the thalidomide-treated groups ($p < 0.001$). There were no significant differences between the control withdrawn and the thalidomide-treated groups. The investigators also compared the total number of occurrences of overt seizures for each treatment group. The rats maintained on sodium barbital and those with substituted pentobarbital had no occurrences of overt seizures. Although substitution with thalidomide did not suppress withdrawal seizures, the thalidomide-treated rats had 16 occurrences of overt seizures during 6 testing sessions compared with 45 occurrences of overt seizures in the control withdrawn rats. The significance of the observed differences between treatment groups in the occurrences of overt seizures was not tested. Thalidomide doses far exceeding those shown to increase deep slow wave sleep and to decrease spontaneous activity in rats did not affect the seizure threshold of physically dependent rats withdrawn from sodium barbital.

In early studies in healthy humans, thalidomide was demonstrated to be a potent CNS depressant in relatively low doses (25 to 100mg) and an effective hypnotic agent in slightly higher doses (100 to 200mg).[125] In contrast to other sedative/hypnotic drugs, thalidomide did not produce an initial excitation phase, and narcotic effects could not be produced, even with very high doses.[125] Thalidomide is believed to induce sleep in humans via dose-related activation of diencephalic (thalamic and hypothalamic) sleep centres.[42,50] Unlike barbiturates, thalidomide does not depress CNS neuronal function,[42] and even at high doses, thalidomide does not cause anaesthesia or respiratory depression.[42] Natural sleep increases the rate of hypersynchrony of discharges from cerebral neurons, resulting in increased risk for epileptiform discharges.[126,127] The somewhat novel sedative/hypnotic mechanism and site of pharmacological action proposed for thalidomide suggest that thalidomide may be a potent CNS depressant, inducing sleep with only minimal suppression of the activity of the cerebral cortex.[42,125]

Thalidomide has been evaluated as a sleep-inducing sedative/hypnotic for sleep-activated electroencephalogram (EEG) studies.[125] Patients with clinically confirmed epilepsy were evaluated with a baseline resting EEG followed by a repeat EEG after a 3- to 5-minute period of hyperventilation. To minimise the potential sources for error, all patients with any electroencephalographic evidence of seizure activity on either the resting EEG or the EEG after hyperventilation were excluded from the thalidomide phase of the study. 99 patients were selected for study, and EEG tracings were again performed between 1 and 2 hours after the administration of a 200mg oral dose of thalidomide. Electroencephalographic evidence of seizure activity (positive result) was detected after the administration of thalidomide in 70 of the 99 cases evaluated (71%). A significant increase in the number of positive results was noted with increasing depth of patient sleep.[125] Under similar investigational conditions thalidomide was evaluated in sleep EEGs among 26 patients with known cerebral tumours who had indeterminate, questionable or negative baseline EEG findings. After a 200mg oral dose of thalidomide, 24 of 26 patients (92%) had demonstrable electrical foci in their EEG patterns corresponding to the locations of the patients' tumours.[125]

In patients predisposed to or at risk of seizure activity, the sedative/hypnotic effect of thalidomide may lower the seizure threshold by facilitating a normal sleep-induced increase in epileptiform discharges without the concurrent suppression of cerebral cortical activity, like that produced by other sedative/hypnotic drugs. During therapy with thalidomide, patients with pre-existing CNS disease or injury, patients at risk for metabolic derangements that may trigger seizure activity, and patients receiving concomitant therapy with potentially epileptogenic agents may need to be monitored closely for clinical changes that could precipitate acute seizure activity. Because of the number of reports of seizures to date, a proposed change to the Thalomid® product labelling has been submitted to the FDA to include a precaution statement regarding the risk of developing seizures during therapy with thalidomide.

3.3.2 Stupor

Six reports have been received in which patients were described with varying levels of 'unresponsiveness' (COSTART: stupor). All of these cases were reported in patients treated for advanced, refractory malignancies. Three patients described as unresponsive were hospitalised for progressive malignancies with fever, neutropenia, sepsis and/or pneumonia and were essentially preterminal. Two patients were described as 'difficult to arouse', and 1 patient presented with a 'decreased level of consciousness'. All of these patients had advanced, progressive malignancies complicated by severe weakness and fatigue, anaemia, nausea and vomiting with dehydration, or tumour lysis syndrome with renal failure. The treating physicians were unsure of the extent to which thalidomide might have contributed to the patients' alterations in level of consciousness. In some cases, thalidomide may have contributed to the reported events by producing excessive somnolence, which is an expected event for

thalidomide. In other cases the events, which were coded as stupor, involved states of unresponsiveness related to complications of the patients' underlying and often preterminal diseases. Although the hypnosedative effects of thalidomide are well characterised, prescription thalidomide is not currently indicated for the treatment of malignancies, and controlled data do not currently exist regarding the occurrence of alterations of consciousness in oncology patients treated with thalidomide. Stupor is not a labelled event included in the current Thalomid® product information. No significant new safety information and no clear reporting trends are identifiable on the basis of the information from spontaneous reports coded as stupor. Because this information is not likely to contribute significantly to the development of the safety profile of thalidomide, further evaluation in a more controlled investigational setting is probably not warranted.

3.3.3 Hallucinations

Five serious postmarketing reports have been received involving hallucinations. All of the patients were treated with thalidomide for malignancies. In 3 patients, episodes involving hallucinations occurred in the setting of acute hospitalisations for fever with sepsis, fever with pneumonia and hypoxia, and anorexia, dehydration and confusion. One patient with refractory multiple myeloma and chronic haemodialysis-dependent renal failure experienced hallucinations associated with increasingly severe uraemia that occurred during an attempt to decrease the frequency of his haemodialysis. The fifth patient developed what was described as an acute psychotic episode with confusion and hallucinations of 48 hours' duration. This episode occurred 2 weeks after therapy with thalidomide had been discontinued. The patient also had a history of 1 previous similar episode associated with the administration of chemotherapy, which had occurred before starting therapy with thalidomide.

Thalidomide has well documented CNS effects. Although hallucinations are not labelled events for Thalomid®, other events with a potentially similar and related pathogenesis that are currently labelled events include abnormal thinking, agitation, confusion, dementia, emotional lability, hostility, mood changes, psychosis, cerebral ischaemia and cerebrovascular accident. Prescription thalidomide is not currently indicated for the treatment of malignancies, and there are currently no controlled data available regarding the incidence of neuropsychiatric events in oncology patients treated with thalidomide. No significant new safety information and no clear reporting trends are identifiable based on the information from spontaneous reports of hallucinations. The current Thalomid® labelling adequately describes neuropsychiatric events potentially associated with thalidomide therapy, and no additional specific investigation is probably warranted at this time.

3.3.4 Hepatic Failure

Four serious postmarketing reports of hepatic failure have been received. In 1 case, a 75-year-old female patient treated with thalidomide for advanced multiple myeloma was hospitalised for severe jaundice and hepatic failure after approximately 1 month of therapy. The patient developed hepatic coma and died. The treating physician felt that because of the temporal relationship between the events and treatment with thalidomide, and because no other cause for the patient's events was identified (an autopsy was not performed), the possibility that the events and the patient's death had been related to treatment could not be excluded. One patient was treated with thalidomide for HIV-related *Mycobacterium avium* complex. The patient, who had severe HIV-related liver disease predating therapy with thalidomide, developed hepatic failure with ascites and died after 6 days of therapy. The treating physician felt that the patient's death was not related to treatment. The third patient was treated for carcinoma of the colon with liver metastases. The patient died as a result of progressive metastatic liver disease with hepatic failure, coagulopathy and gastrointestinal bleeding, which the treating physician felt were not related to therapy. In the fourth case, a patient with pre-existing systemic lupus erythematosus was treated with thalidomide for renal cell carcinoma. This patient, who had a history of lupus nephritis, renal failure and

hepatic failure predating therapy, died after approximately 3 weeks of therapy with thalidomide as a result of progressive renal and hepatic failure, which the treating physician felt were unrelated to treatment.

Hepatic failure is an unexpected event for thalidomide. The safety, efficacy and pharmacokinetics of thalidomide have not been specifically studied in patients with hepatic dysfunction. Increased liver function tests were reported in 2.8 to 12.5% of HIV-seropositive patients treated with thalidomide in controlled clinical trials (n = 68). Increased liver function tests, bilirubinaemia and hepatomegaly were also reported from uncontrolled investigational experience with thalidomide in 3143 patients with ENL in the US over a 19-year period.[32,45] Other hepatic events reported from the uncontrolled investigational use of thalidomide in 145 HIV-seropositive patients and from additional events identified in the published literature or from spontaneous reports from other sources involving the investigational use of thalidomide in various other indications have included cholestatic jaundice, hepatitis, bilirubinaemia and bile duct obstruction.[32,45] Because these data came from uncontrolled investigational clinical experience, the true incidence rate for the reported events cannot be determined, and no causal relationship between the reported events and treatment with thalidomide can be conclusively determined. In refractory multiple myeloma, no adverse hepatic effects were reported.[49] There are currently no controlled data available regarding the incidence of increased liver function tests or hepatic failure in oncology patients treated with thalidomide.

Thalidomide does not undergo significant hepatic enzyme-dependent metabolism.[32,40,41] In aqueous solution at physiological pH, thalidomide decomposes by spontaneous hydrolysis.[41] In Celgene Corporation-sponsored *in vitro* studies using a large range of human cloned CYP enzymes, rat liver homogenates and human liver homogenates, thalidomide was shown to be a poor substrate for CYP-dependent mono-oxygenase reactions, with negligible thalidomide metabolism by CYP isozymes. Thalidomide also did not inhibit the metabolism of any CYP isozyme-specific substrates.[32,40]

The safety, efficacy and pharmacokinetics of thalidomide have not been specifically studied in patients with hepatic dysfunction. Thalidomide therapy was evaluated in a double-blind, placebo-controlled pilot study in primary biliary cirrhosis. The mean baseline serum bilirubin for patients receiving thalidomide in this study was 11 mg/dl. After 6 months of therapy with thalidomide 100 mg/day, no significant effects on hepatic histology or biochemical tests of liver function were noted.[128]

As with many of the serious unexpected events reported for prescription thalidomide, the majority of the reports of hepatic failure involved complications of the patients' severe, advanced underlying diseases. No significant new safety information and no clear reporting trends are identifiable from spontaneous reports of hepatic failure received to date.

3.3.5 Coma

Three serious spontaneous cases involving coma have been reported for thalidomide. In 1 case, a 78-year-old woman with progressive multiple myeloma and pre-existing renal insufficiency was treated with thalidomide 300 mg/day. Therapy was discontinued after 2 days because of excessive sedation. Four days after thalidomide was discontinued, the patient became progressively less responsive, eventually comatose, and died. The treating physician assumed that the patient's death was attributable to progressive multiple myeloma with kidney disease but felt that it was not exactly clear why the patient had progressed into a comatose state. A second patient with progressive multiple myeloma was being treated with dexamethasone at the time that therapy with thalidomide 200 mg/day was initiated. Before starting therapy, the patient had a several-week history of mental status changes, generalised weakness, urinary frequency and dysuria. After 9 days of therapy with thalidomide, the patient presented in an obtunded state diagnosed as diabetic coma. The treating physician assessed the patient's events to have been unrelated to therapy. The third patient was treated with thalidomide for

end-stage cystic lymphangiomatosis. After 2 months of therapy with thalidomide 600 mg/day and concomitant interferon, the patient developed fever, mental status changes, and seizures suggestive of mild septic shock. The patient was brought to the hospital 'unconscious' (COSTART: coma) during the postictal period. Thalidomide and interferon therapy were discontinued. An MRI scan of the head was possibly consistent with changes from previous radiation therapy versus acute disseminated encephalomyelitis or lymphoma. The patient had a history of herpes simplex keratitis and was treated for possible herpes encephalitis. Two months after therapy with thalidomide had been discontinued, the patient was again hospitalised with increased seizure activity and mental status changes felt possibly to be due to chronic changes from his underlying malignancy. No causality assessment was provided for the patient's events.

All of the spontaneous reports of coma submitted to date have been for patients treated for malignancies. Thalomid® is not currently indicated for the treatment of malignancies, and there are no controlled data available regarding the incidence of neurological events in oncology patients treated with thalidomide. The reported patients had other underlying conditions, which may have predisposed them to neurological events including the events described as coma. One report involved an event which occurred after the discontinuation of thalidomide, and 1 report appears to have been related to a postictal state following seizure activity. A detailed discussion of seizures associated with thalidomide therapy has already been presented. The third report of coma involved complications of an underlying pre-existing condition. No significant new safety information and no clear reporting trends are identifiable from spontaneous reports of coma received to date.

3.3.6 Stevens-Johnson Syndrome

Three postmarketing cases of Stevens-Johnson syndrome have been spontaneously reported for patients with malignancies (multiple myeloma, lymphoma and ovarian cancer) treated with thalidomide (CRR 0.03%). One of these reports involved a patient death.

Two reports of thalidomide-induced TEN have been identified from the published literature.[55,56] In a clinical study evaluating thalidomide as therapy for TEN, thalidomide was ineffective in halting the necrolysis process during the initial phase of extension. Increased mortality due to multiple organ failure, sepsis, shock and acute respiratory distress syndrome was also reported for patients with TEN treated with thalidomide.[129]

Because of reports of Stevens-Johnson syndrome and TEN in patients treated with thalidomide, the Thalomid® product labelling has been changed to include a precaution statement indicating that serious dermatological reactions including Stevens-Johnson syndrome, which may be fatal, have been reported. The revised labelling recommends that thalidomide should be discontinued if a skin rash occurs and resumed only after appropriate clinical evaluation. If the rash is exfoliative, purpuric or bullous or if Stevens-Johnson syndrome or TEN is suspected, use of thalidomide should not be resumed.

3.3.7 Skin Ulcers

Although 'skin necrosis' is a labelled event included in the current Thalomid® product information, skin ulcers or decubitus ulcers are not specifically included as labelled events. Skin necrosis was not reported from clinical trials of thalidomide in patients with ENL or in HIV-seropositive patients, but was reported in the published literature of uncontrolled investigational experience with the use of thalidomide in patients with ENL.[32,45] Because this information came from data collected in uncontrolled trials, the true incidence rate for the reported event cannot be determined, and no causal relationship between the reported event and treatment with thalidomide can be conclusively determined.

Three spontaneous cases of skin ulcer have been reported (CRR 0.03%). These reports include 2 patients treated with thalidomide for graft versus host disease (GVHD) and 1 patient treated for multiple myeloma. One patient with GVHD, a 51-year-old

woman, was treated with thalidomide 600 mg/day after a bone marrow transplant for chronic lymphocytic leukaemia. The patient had leg ulcers predating therapy with thalidomide. After approximately 8 months of therapy, she was hospitalised for worsening leg ulcers. Thalidomide was discontinued, and the patient was treated with surgical debridement, rehabilitation and wound care and an improvement was observed.

The second patient with GVHD, a 42-year-old woman with GVHD after a bone marrow transplant for chronic lymphocytic leukaemia, was treated with thalidomide 600 mg/day. After approximately 9 months of therapy, the patient developed debilitating leg ulcers requiring hospitalisation. Thalidomide was discontinued. Two months after discontinuing therapy, the patient died of pneumonia.

A 56-year-old female patient with multiple myeloma had decubitus ulcers on her back and hip prior to starting therapy with thalidomide. After 14 days of thalidomide 400 mg/day, her decubitus ulcers were felt to have become worse. The treating physician noted that the patient had also been significantly less mobile during this period. Therapy was discontinued, and the patient was hospitalised for surgical debridement of a necrotic sacral decubitus ulcer.

The establishment of a vascular supply or angiogenesis is an essential process during fetal development. In the adult, normal angiogenesis is required for reproductive functions (menstruation, placental development, formation of the corpus luteum) and tissue repair after wounding or inflammation.[130-132] Angiogenesis is also a prerequisite for rapid tumour growth and metastasis[25-29] and contributes to a number of other pathological conditions, including diabetic retinopathy, rheumatoid arthritis, haemangiomas, psoriasis, ischaemic heart disease, atherosclerosis and gastric ulcers.[25,27,133] The control of angiogenesis involves a balance of positive and negative regulators, which control whether vascular wall cells remain in a state of homeostasis or proceed to neovascularisation. A large number of angiogenic and antiangiogenic factors have been identified and characterised.[28,29,131,133] bFGF is a potent endogenous angiogenic protein among the most important stimulatory factors in both tumour growth and metastasis[29,133] and in wound healing.[134,135] Orally administered thalidomide has been shown in several animal models to be an inhibitor of angiogenesis induced by bFGF.[23,24] Thalidomide is currently under investigation as an inhibitor of angiogenesis in humans for the treatment of tumours that are not responsive to standard therapy. There are currently, however, no controlled data regarding the effects, if any, of thalidomide on wound healing in humans.

Preliminary studies of the immunomodulatory effects of thalidomide in animal models have not demonstrated inhibition or other disturbances of wound healing associated with orally administered thalidomide. In a guinea-pig model of angiogenesis in experimentally induced granulomata, orally administered thalidomide exerted a dual effect. Following the subcutaneous implantation of polyvinyl alcohol sponges in guinea-pigs, treatment with thalidomide significantly reduced vascular density ($p < 0.05$) and at the same time enhanced the granulomatous response, improving wound healing and scar formation ($p < 0.05$).[136] In a second study in mongrel dogs, thalidomide was used to replace corticosteroids for immunosuppression after lung transplantation. Three postoperative immunosuppressive regimens were evaluated. Maintenance immunosuppressive therapy was started 12 hours after extubation. Treatment group I received cyclosporin (20 mg/kg twice daily), azathioprine (2.5 mg/kg once daily) and thalidomide (50 mg/kg twice daily). Treatment group II received standard immunosuppression with cyclosporin (20 mg/kg twice daily), azathioprine (2.5 mg/kg once daily) and prednisone (2 mg/kg once daily). The third treatment group (group III) received cyclosporin (10 mg/kg twice daily), azathioprine (2.5 mg/kg once daily) and thalidomide (50 mg/kg twice daily). After transplantation, the animals were evaluated weekly with open lung biopsies and bronchoscopy until sacrifice on day 28. Group I showed essentially no graft rejection until week 2 and minimal (grade 1) rejection until day 28.

Group II had moderate (grade 2) rejection at all time points.[137]

The group III animals had moderate to severe rejection (grades 3 to 4) after 21 days ($p < 0.05$ group I *vs* groups II and III). The number of clinically evident episodes of pneumonia was also significantly lower in group I than in groups II and III ($p < 0.05$). The major postoperative complications involved disturbances of wound healing with wound dehiscences at the thoracotomy sites. None of the dogs in group I experienced partial or complete wound dehiscence. Partial wound dehiscence occurred in 3 of 5 dogs in group II and in 1 of 5 dogs in group III. The investigators concluded that thalidomide administered after single lung transplantation was associated with decreased acute rejection, decreased episodes of pulmonary infections and a lower incidence of wound healing disturbances and bronchial stenosis, when compared with standard immunosuppressive therapy.[137]

A recently published case report describes an example of successful skin grafting performed on a patient taking thalidomide who had generalised morphea, a degenerative, fibrotic dermatological disorder.[138] The authors noted that, despite the concern that thalidomide's potential anti-inflammatory, antifibrotic and antiangiogenic effects could theoretically become a liability in successful wound heaing, this patient healed well after skin grafting with no interruption in thalidomide therapy (800 to 1000 mg/day).

Thalidomide is not currently approved for the treatment of malignancies, and no controlled data are available regarding the occurrence of skin necrosis, skin ulcers or abnormal healing in oncology patients treated with thalidomide. With the use of prescription thalidomide in patient populations that may be at risk for wound complications, continued close monitoring of the spontaneous postmarketing safety surveillance data may help to better define the effects of thalidomide on wound healing and to identify specific risk factors associated with wound complications. In the absence of controlled data specific to thalidomide, it may be prudent to apply the current recommendations for the use of chemotherapeutic agents and/or radiation therapy to the use of thalidomide in situations where wound complications may be expected. It is well established that chemotherapy and radiation therapy inhibit wound healing. Early studies in animal models demonstrated that the timing and the combination of multiple antineoplastic agents were critical to the effects on wound healing. These studies suggested that radiation or antineoplastic drugs delivered 5 to 7 days before or after a surgical procedure resulted in minimal inhibition of wound healing. Conversely, the administration of radiation or chemotherapy in close juxtaposition to the time of surgery resulted in significant impairment of wound healing, as demonstrated by wound breaking strength.[139] As predicted by the animal studies, when particular attention is paid to the timing of the administration of radiation and or chemotherapy, wound complications can be markedly diminished.[140] Chemotherapeutic agents should not generally be administered until at least 5 to 7 days postoperatively to prevent impairment of the initial, critical healing events.[141]

3.3.8 Paranoid Reaction

Three spontaneous postmarketing cases of paranoid reaction have been reported. All 3 patients were treated with thalidomide for multiple myeloma. One patient experienced auditory hallucinations and paranoid ideation in the setting of an acute hospitalisation for anorexia, dehydration and confusion after more than 1 year of therapy with thalidomide 200 mg/day. The second patient was receiving concomitant therapy with high dose dexamethasone and had a past history significant for previous episodes of bizarre behaviour associated with corticosteroid therapy. The patient required acute psychiatric hospitalisation for bizarre behaviour with paranoia after 29 days of therapy with thalidomide 400 mg/day and 23 days of therapy with dexamethasone. The third patient was hospitalised for paranoid ideation after approximately 8 months of therapy with thalidomide 200 mg/day. Causality assessments were not provided for these 3 cases. All 3 patients discontinued therapy with thalidomide.

Thalidomide has well documented CNS effects. Although paranoid reaction is not a labelled event for Thalomid®, other events with a potentially similar and related pathogenesis that are currently labelled events include abnormal thinking, agitation, confusion, dementia, emotional lability, hostility, mood changes, psychosis, cerebral ischaemia and cerebrovascular accident. Prescription thalidomide is not currently indicated for the treatment of multiple myeloma or other malignancies, and there are no controlled data available regarding the incidence of neuropsychiatric events in oncology patients treated with thalidomide. No significant new safety information and no clear reporting trends are identifiable based on the information from spontaneous reports of paranoid reaction. The current Thalomid® labelling adequately describes neuropsychiatric events potentially associated with thalidomide therapy, and no additional specific investigation is probably warranted.

4. Conclusions

18 months of spontaneous postmarketing safety surveillance have now been completed for Thalomid® capsules. The most common adverse events spontaneously reported for prescription thalidomide have been somnolence, asthenia, rash, peripheral oedema, paraesthesia, dizziness, constipation, dyspnoea and leucopenia. All of these adverse events would have been expected on the basis of the current Thalomid® labelling/product information. Although thalidomide is not known to have any specific drug-drug interactions, the possibility that the adverse effects of thalidomide may be additive with those of other drugs with similar effects cannot be excluded. In some cases, it may be helpful to evaluate adverse reactions and make therapeutic decisions relative to the individual patient's entire medication regimen.

Thalidomide has been reported to depress thyroid secretory activity, and cases of hypothyroidism have been reported.[33,42,43,63-65] The potential contribution of subclinical hypothyroidism to the adverse effects attributed directly to thalidomide is currently unknown. It may be prudent to perform thyroid function testing in patients with persistent symptoms or first onset of symptoms after prolonged therapy with thalidomide.

Thromboembolic adverse events have previously been reported in association with thalidomide therapy. With the use of prescription thalidomide in patient populations that may be particularly susceptible to thromboembolic phenomena, consideration of the spontaneous postmarketing safety surveillance data may help to identify patient groups and other factors associated with increased risk. In particular, patients with malignancies may represent a population with increased susceptibility to thromboembolic events. A number of controlled clinical trials are currently in progress to investigate the effects of thalidomide on the coagulation system in non-anticoagulated patients.

In patients predisposed to or at risk for seizure activity, the sedative/hypnotic effect of thalidomide may lower the seizure threshold by facilitating a normal sleep-induced increase in epileptiform discharges without the concurrent suppression of cerebral cortical activity, which is produced by other sedative/hypnotic drugs. During therapy with thalidomide, patients with pre-existing CNS disease or injury, patients at risk for metabolic derangements that may trigger seizure activity, and patients receiving concomitant therapy with potentially epileptogenic agents may require close monitoring for clinical changes that could precipitate acute seizure activity.

Because serious dermatological reactions including Stevens-Johnson syndrome and TEN, which may be fatal, have been reported, patients who develop rash during therapy with thalidomide should have prompt medical evaluation. If clinically appropriate, thalidomide therapy should be discontinued. If the rash is exfoliative, purpuric or bullous or if Stevens-Johnson syndrome or TEN is suspected, use of thalidomide should not be resumed.

Thalidomide has well documented CNS effects. Therapy with thalidomide may potentially contribute to a variety of adverse neuropsychiatric events and alterations of consciousness, many of which

are described in the current Thalomid® labelling/product information.

Angiogenesis is an important process involved in tissue repair after wounding or inflammation. Orally administered thalidomide has been shown in animal models to be an inhibitor of angiogenesis. Thalidomide is currently under investigation as an inhibitor of angiogenesis in humans for the treatment of tumours that are not responsive to standard therapy. There are currently, however, no controlled data regarding the effects, if any, of thalidomide on wound healing in humans. Continued close monitoring of spontaneous postmarketing safety surveillance data may help to better define the effects of thalidomide on wound healing and to identify specific risk factors associated with wound complications. In the absence of controlled data specific to thalidomide, it may be prudent to apply the current recommendations for the use of chemotherapeutic agents and/or radiation therapy to the use of thalidomide in situations where wound complications may be likely.

With the postmarketing use of thalidomide in patient populations other than patients with ENL, it becomes increasingly important to identify patient groups that may be particularly susceptible to specific adverse drug effects and to identify conditions under which specific adverse events may be more likely to occur. Vigilant monitoring of unexpected adverse events not previously reported in association with thalidomide therapy may lead to the identification of signals of potential new problems that warrant further investigation and hypothesis generation for testing in more controlled settings. The development of the safety profile of any drug product is an evolving process. As with any marketed drug, in order to provide guidance for the judicious use of thalidomide in current clinical practice as well as in the investigational setting, the accumulation and analysis of broader population experience with thalidomide through postmarketing safety surveillance is critical for the ongoing development of an accurate and clinically relevant safety profile. Accurate and up-to-date safety information will be important in determining thalidomide's appropriate place in therapy, as new therapeutic indications are considered and investigated.

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