

1
2 **PROPOSED CHANGES TO APPROVED THALOMID® PACKAGE INSERT**
3 Highlighted Version
4

5 **THALOMID® (thalidomide) Capsules 50 mg, 100 mg, & 200mg**

6 **WARNING: SEVERE, LIFE-THREATENING HUMAN BIRTH DEFECTS.**

7 **IF THALIDOMIDE IS TAKEN DURING PREGNANCY, IT CAN CAUSE**
8 **SEVERE BIRTH DEFECTS OR DEATH TO AN UNBORN BABY.**

9 **THALIDOMIDE SHOULD NEVER BE USED BY WOMEN WHO ARE**
10 **PREGNANT OR WHO COULD BECOME PREGNANT WHILE TAKING THE**
11 **DRUG. EVEN A SINGLE DOSE [1 CAPSULE (50 mg, 100 mg or 200 mg)]**
12 **TAKEN BY A PREGNANT WOMAN DURING HER PREGNANCY CAN**
13 **CAUSE SEVERE BIRTH DEFECTS.**

14 **BECAUSE OF THIS TOXICITY AND IN AN EFFORT TO MAKE THE**
15 **CHANCE OF FETAL EXPOSURE TO THALOMID® (thalidomide) AS**
16 **NEGLIGIBLE AS POSSIBLE, THALOMID® (thalidomide) IS APPROVED FOR**
17 **MARKETING ONLY UNDER A SPECIAL RESTRICTED DISTRIBUTION**
18 **PROGRAM APPROVED BY THE FOOD AND DRUG ADMINISTRATION.**
19 **THIS PROGRAM IS CALLED THE "SYSTEM FOR THALIDOMIDE**
20 **EDUCATION AND PRESCRIBING SAFETY (S.T.E.P.S.®)."**

21 **UNDER THIS RESTRICTED DISTRIBUTION PROGRAM, ONLY**
22 **PRESCRIBERS AND PHARMACISTS REGISTERED WITH THE PROGRAM**
23 **ARE ALLOWED TO PRESCRIBE AND DISPENSE THE PRODUCT. IN**
24 **ADDITION, PATIENTS MUST BE ADVISED OF, AGREE TO, AND COMPLY**
25 **WITH THE REQUIREMENTS OF THE S.T.E.P.S.® PROGRAM IN ORDER TO**
26 **RECEIVE PRODUCT.**

27 **PLEASE SEE THE FOLLOWING BOXED WARNINGS CONTAINING**
28 **SPECIAL INFORMATION FOR PRESCRIBERS, FEMALE PATIENTS, AND**
29 **MALE PATIENTS ABOUT THIS RESTRICTED DISTRIBUTION PROGRAM.**

30
31 **PRESCRIBERS**

32 THALOMID® (thalidomide) may be prescribed only by licensed prescribers who are
33 registered in the S.T.E.P.S.® program and understand the risk of teratogenicity if
34 thalidomide is used during pregnancy.

35 Major human fetal abnormalities related to thalidomide administration during
36 pregnancy have been documented: amelia (absence of limbs), phocomelia (short
37 limbs), hypoplasticity of the bones, absence of bones, external ear abnormalities
38 (including anotia, micro pinna, small or absent external auditory canals), facial palsy,
39 eye abnormalities (anophthalmos, microphthalmos), and congenital heart defects.
40 Alimentary tract, urinary tract, and genital malformations have also been documented.¹
41 Mortality at or shortly after birth has been reported at about 40%.²

42 Effective contraception (see **CONTRAINDICATIONS**) must be used for at least 4
 43 weeks before beginning thalidomide therapy, during thalidomide therapy, and for 4
 44 weeks following discontinuation of thalidomide therapy. Reliable contraception is
 45 indicated even where there has been a history of infertility, unless due to hysterectomy
 46 or because the patient has been postmenopausal for at least 24 months. Two reliable
 47 forms of contraception must be used simultaneously unless continuous abstinence from
 48 heterosexual sexual contact is the chosen method. Women of childbearing potential
 49 should be referred to a qualified provider of contraceptive methods, if needed. Sexually
 50 mature women who have not undergone a hysterectomy or who have not been
 51 postmenopausal for at least 24 consecutive months (i.e., who have had menses at some
 52 time in the preceding 24 consecutive months) are considered to be women of
 53 childbearing potential.

54 **Before starting treatment**, women of childbearing potential should have a pregnancy
 55 test (sensitivity of at least 50 mIU/mL). The test should be performed within the 24
 56 hours prior to beginning thalidomide therapy. A prescription for thalidomide for a
 57 woman of childbearing potential must not be issued by the prescriber until a written
 58 report of a negative pregnancy test has been obtained by the prescriber.

59 *Male Patients:* Because thalidomide is present in the semen of patients receiving the
 60 drug, males receiving thalidomide must always use a latex condom during any sexual
 61 contact with women of childbearing potential even if he has undergone a successful
 62 vasectomy.

63 **Once treatment has started**, pregnancy testing should occur weekly during the first 4
 64 weeks of use, then pregnancy testing should be repeated at 4 weeks in women with
 65 regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should
 66 occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient
 67 misses her period or if there is any abnormality in menstrual bleeding.

68 If pregnancy does occur during thalidomide treatment, thalidomide must be
 69 discontinued immediately.

70 Any suspected fetal exposure to THALOMID[®] (thalidomide) must be reported
 71 immediately to the FDA *via* the MedWatch number at 1-800-FDA-1088 and also to
 72 Celgene Corporation. The patient should be referred to an obstetrician/gynecologist
 73 experienced in reproductive toxicity for further evaluation and counseling.

74

FEMALE PATIENTS

75
 76 Thalidomide is contraindicated in WOMEN of childbearing potential unless alternative
 77 therapies are considered inappropriate AND the patient MEETS ALL OF THE
 78 FOLLOWING CONDITIONS (i.e., she is essentially unable to become pregnant while
 79 on thalidomide therapy):

- 80 • she understands and can reliably carry out instructions
- 81 • she is capable of complying with the mandatory contraceptive measures,
 82 pregnancy testing, patient registration, and patient survey as described in the

- 83 System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*[®])
 84 program.
- 85 • she has received both oral and written warnings of the hazards of taking
 86 thalidomide during pregnancy and of exposing a fetus to the drug.
 - 87 • she has received both oral and written warnings of the risk of possible
 88 contraception failure and of the need to use two reliable forms of contraception
 89 simultaneously (see **CONTRAINDICATIONS**), unless continuous abstinence
 90 from heterosexual sexual contact is the chosen method. Sexually mature women
 91 who have not undergone a hysterectomy or who have not been postmenopausal
 92 for at least 24 consecutive months (i.e., who have had menses at some time in
 93 the preceding 24 consecutive months) are considered to be women of
 94 childbearing potential.
 - 95 • she acknowledges, in writing, her understanding of these warnings and of the
 96 need for using two reliable methods of contraception for 4 weeks prior to
 97 beginning thalidomide therapy, during thalidomide therapy, and for 4 weeks
 98 after discontinuation of thalidomide therapy.
 - 99 • she has had a negative pregnancy test with a sensitivity of at least 50 mIU/mL,
 100 within the 24 hours prior to beginning therapy. (See **PRECAUTIONS**,
 101 **CONTRAINDICATIONS**.)
 - 102 • if the patient is between 12 and 18 years of age, her parent or legal guardian
 103 must have read this material and agreed to ensure compliance with the above.

104

MALE PATIENTS

105
 106 Thalidomide is contraindicated in sexually mature MALES unless the PATIENT
 107 MEETS ALL OF THE FOLLOWING CONDITIONS:

- 108 • he understands and can reliably carry out instructions.
- 109 • he is capable of complying with the mandatory contraceptive measures that are
 110 appropriate for men, patient registration, and patient survey as described in the
 111 *S.T.E.P.S.*[®] program.
- 112 • he has received both oral and written warnings of the hazards of taking
 113 thalidomide and exposing a fetus to the drug.
- 114 • he has received both oral and written warnings of the risk of possible
 115 contraception failure and of the presence of thalidomide in semen. He has been
 116 instructed that he must always use a latex condom during any sexual contact
 117 with women of childbearing potential, even if he has undergone a successful
 118 vasectomy.
- 119 • he acknowledges, in writing, his understanding of these warnings and of the
 120 need to use a latex condom during any sexual contact with women of
 121 childbearing potential, even if he has undergone a successful vasectomy.
 122 Sexually mature women who have not undergone a hysterectomy or who have

not been postmenopausal for at least 24 consecutive months (i.e., who have had menses at any time in the preceding 24 consecutive months) are considered to be women of childbearing potential.

- if the patient is between 12 and 18 years of age, his parent or legal guardian must have read this material and agreed to ensure compliance with the above.

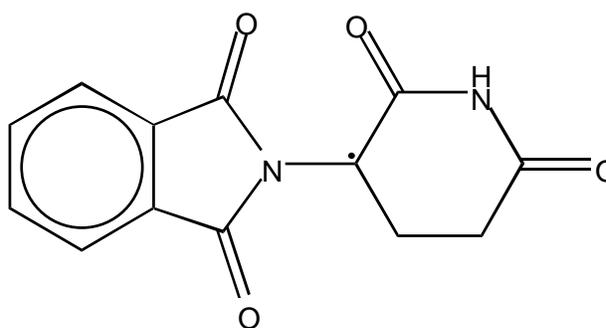
Venous Thromboembolic Events

The use of Thalomid[®] (thalidomide) in multiple myeloma results in an increased risk of venous thromboembolic events, such as deep venous thrombosis and pulmonary embolus. This risk increases significantly when thalidomide is used in combination with standard chemotherapeutic agents including dexamethasone. In one controlled trial, the rate of venous thromboembolic events was 22.5% in patients receiving thalidomide in combination with dexamethasone compared to 4.9% in patients receiving dexamethasone alone ($p = 0.002$). Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Preliminary data suggest that patients who are appropriate candidates may benefit from concurrent prophylactic anticoagulation or aspirin treatment.

DESCRIPTION

THALOMID[®] (thalidomide), α -(N-phthalimido) glutarimide, is an immunomodulatory agent. The empirical formula for thalidomide is $C_{13}H_{10}N_2O_4$ and the gram molecular weight is 258.2. The CAS number of thalidomide is 50-35-1.

Chemical Structure of thalidomide



Note: • = asymmetric carbon atom

Thalidomide is an off-white to white, odorless, crystalline powder that is soluble at 25°C in dimethyl sulfoxide and sparingly soluble in water and ethanol. The glutarimide moiety contains a single asymmetric center and, therefore, may exist in either of two optically active forms designated S-(-) or R-(+). THALOMID[®] (thalidomide) is an

165 equal mixture of the S-(-) and R-(+) forms and, therefore, has a net optical rotation of
166 zero.

167 THALOMID[®] (thalidomide) is available in 50 mg, 100 mg and 200 mg capsules for
168 oral administration. Active ingredient: thalidomide. Inactive ingredients: pregelatinized
169 starch and magnesium stearate. The 50 mg capsule shell contains gelatin, titanium
170 dioxide, and black ink. The 100 mg capsule shell contains black iron oxide, yellow iron
171 oxide, titanium dioxide, gelatin, and black ink. The 200 mg capsule shell contains
172 FD&C blue #2, titanium dioxide, gelatin, and white ink.

173 **CLINICAL PHARMACOLOGY**

174 **Mechanism of Action**

175 The mechanism of action of thalidomide is not fully understood. Thalidomide
176 possesses immunomodulatory, anti-inflammatory and anti-angiogenic properties.
177 Available data from in vitro studies and clinical trials suggest that the immunologic
178 effects of this compound can vary substantially under different conditions, but may be
179 related to suppression of excessive tumor necrosis factor-alpha (TNF- α) production and
180 down-modulation of selected cell surface adhesion molecules involved in leukocyte
181 migration.³⁻⁶ For example, administration of thalidomide has been reported to decrease
182 circulating levels of TNF- α in patients with erythema nodosum leprosum (ENL)³,
183 however, it has also been shown to increase plasma TNF- α levels in HIV-seropositive
184 patients.⁷ Other anti-inflammatory and immunomodulatory properties of thalidomide
185 may include suppression of macrophage involvement in prostaglandin synthesis, and
186 modulation of interleukin-10 and interleukin-12 production by peripheral blood
187 mononuclear cells. Thalidomide treatment of multiple myeloma patients is
188 accompanied by an increase in the number of circulating natural killer cells, and an
189 increase in plasma levels of interleukin-2 and interferon-gamma (T cell-derived
190 cytokines associated with cytotoxic activity). Thalidomide was found to inhibit
191 angiogenesis in a human umbilical artery explant model *in vitro*. The cellular
192 processes of angiogenesis inhibited by thalidomide may include the proliferation of
193 endothelial cells.

194

195 **Pharmacokinetics and Drug Metabolism**

196 **Absorption**

197 The absolute bioavailability of thalidomide from THALOMID[®] (thalidomide) capsules
198 has not yet been characterized in human subjects due to its poor aqueous solubility.
199 However, the capsules are 90% bioavailable relative to an oral PEG solution. In studies
200 of both healthy volunteers and subjects with Hansen's disease, the mean time to peak
201 plasma concentrations (T_{max}) of THALOMID[®] (thalidomide) ranged from 2.9 to 5.7
202 hours indicating that THALOMID[®] (thalidomide) is slowly absorbed from the
203 gastrointestinal tract. While the extent of absorption (as measured by area under the
204 curve [AUC]) is proportional to dose in healthy subjects, the observed peak
205 concentration (C_{max}) increased in a less than proportional manner (see Table 1 below).
206 This lack of C_{max} dose proportionality, coupled with the observed increase in T_{max}

207 values, suggests that the poor solubility of thalidomide in aqueous media may be
208 hindering the rate of absorption.

209

| Population/ Single Dose | AUC_{0∞} μg•hr/mL | C_{max} μg/mL | T_{max} (hrs) | Half-life (hrs) |
|--------------------------------------|--------------------------------------|----------------------------------|----------------------------------|----------------------------|
| Healthy Subjects (n=14) | | | | |
| 50 mg | 4.9 (16%) | 0.62 (52%) | 2.9 (66%) | 5.52 (37%) |
| 200 mg | 18.9 (17%) | 1.76 (30%) | 3.5 (57%) | 5.53 (25%) |
| 400 mg | 36.4 (26%) | 2.82 (28%) | 4.3 (37%) | 7.29 (36%) |
| Patients with Hansen's Disease (n=6) | | | | |
| 400 mg | 46.4 (44.1%) | 3.44 (52.6%) | 5.7 (27%) | 6.86 (17%) |

210 Coadministration of THALOMID[®] (thalidomide) with a high fat meal causes minor
211 (<10%) changes in the observed AUC and C_{max} values; however, it causes an increase
212 in T_{max} to approximately 6 hours.

213 ***Distribution***

214 In human blood plasma, the geometric mean plasma protein binding was 55% and 66%,
215 respectively, for (+)-(R)- and (-)-(S)-thalidomide.⁸ In a pharmacokinetic study of
216 thalidomide in HIV-seropositive adult male subjects receiving thalidomide 100 mg/day,
217 thalidomide was detectable in the semen.

218 ***Metabolism***

219 At the present time, the exact metabolic route and fate of thalidomide is not known in
220 humans. Thalidomide itself does not appear to be hepatically metabolized to any large
221 extent, but appears to undergo non-enzymatic hydrolysis in plasma to multiple products.
222 In a repeat dose study in which THALOMID[®] (thalidomide) 200 mg was administered
223 to 10 healthy females for 18 days, thalidomide displayed similar pharmacokinetic
224 profiles on the first and last day of dosing. This suggests that thalidomide does not
225 induce or inhibit its own metabolism.

226 ***Elimination***

227 As indicated in Table 1 (above) the mean half-life of elimination ranges from
228 approximately 5 to 7 hours following a single dose and is not altered upon multiple
229 dosing. As noted in the metabolism subsection, the precise metabolic fate and route of
230 elimination of thalidomide in humans is not known at this time. Thalidomide itself has a
231 renal clearance of 1.15 mL/minute with less than 0.7% of the dose excreted in the urine
232 as unchanged drug. Following a single dose, urinary levels of thalidomide were
233 undetectable 48 hrs after dosing. Although thalidomide is thought to be hydrolyzed to a
234 number of metabolites⁹ only a very small amount (0.02% of the administered dose) of
235 4-OH-thalidomide was identified in the urine of subjects 12 to 24 hours after dosing.

236 ***Pharmacokinetic Data in Special Populations***

237 *HIV-seropositive Subjects:* There is no apparent significant difference in measured
238 pharmacokinetic parameter values between healthy human subjects and HIV-
239 seropositive subjects following single dose administration of THALOMID[®]
240 (thalidomide) capsules.

241 *Patients with Hansen's Disease:* Analysis of data from a small study in Hansen's
242 patients suggests that these patients, relative to healthy subjects, may have an increased
243 bioavailability of THALOMID[®] (thalidomide). The increase is reflected both in an
244 increased area under the curve and in increased peak plasma levels. The clinical
245 significance of this increase is unknown.

246 *Patients with Renal Insufficiency:* The pharmacokinetics of thalidomide in patients with
247 renal impairment have not been determined. In a study of 6 patients with end-stage
248 renal disease, thalidomide (200 mg/day) was administered on a non-dialysis day and on
249 a dialysis day. Comparison of concentration-time profiles on a non-dialysis day and
250 during dialysis where blood samples were collected at least 10 hours following the dose,
251 showed that the mean total clearance increased by a factor of 2.5 during hemodialysis.
252 Because the dialysis was performed 10 hours following administration of the dose, the
253 drug-concentration time curves were not statistically significantly different for days
254 patients were on and off of dialysis. Thus, no dosage adjustment is needed for renally-
255 impaired patients on dialysis.

256 *Patients with Hepatic Disease:* The pharmacokinetics of thalidomide in patients with
257 hepatic impairment have not been determined.

258 *Age:* Analysis of the data from pharmacokinetic studies in healthy volunteers and
259 patients with Hansen's disease ranging in age from 20 to 69 years does not reveal any
260 age-related changes.

261 *Pediatric:* No pharmacokinetic data are available in subjects below the age of 18 years.

262 *Gender:* While a comparative trial of the effects of gender on thalidomide
263 pharmacokinetics has not been conducted, examination of the data for thalidomide does
264 not reveal any significant gender differences in pharmacokinetic parameter values.

265 *Race:* Pharmacokinetic differences due to race have not been studied.

266 *Clinical Studies*

267 **Clinical Study in Multiple Myeloma:**

268 The efficacy of THALOMID[®] in multiple myeloma was demonstrated in a randomized,
269 multi-center open-label study of 207 newly diagnosed patients. This study randomized
270 symptomatic patients with newly diagnosed multiple myeloma to THALOMID[®] plus
271 dexamethasone (Thal + Dex; N = 103) versus dexamethasone alone (Dex alone;
272 N=104). The THALOMID dose was 200 mg daily and the dexamethasone dose was 40
273 mg orally once daily on days 1-4, 9-12, and 17-20 every 28-days. Each group was
274 treated for four 28-day cycles.

275 Baseline demographic and disease characteristics for the study population are
276 summarized in Tables 2 and 3 respectively.

277

278

| Table 2 | | |
|--------------------------------------|-------------------------------|------------------------------|
| Baseline Patient Demographics | | |
| Characteristic | Thal + Dex (N=103) | Dex alone (N=104) |
| Age (years) | | |
| Median | 65 | 68 |
| Range | 37 – 83 | 38 – 83 |
| Gender¹ | | |
| Male | 53 (51%) | 61 (59%) |
| Female | 50 (49%) | 42 (40%) |
| Race² | | |
| Caucasian | 90 (87%) | 90 (87%) |
| Black | 11 (11%) | 11 (11%) |
| Other | 1 (1%) | 2 (2%) |

279
280
281
282

¹Missing information for 1 patient in the Dex alone group
²Missing information for 1 patient per arm

| Table 3 | | |
|--|-------------------------------|------------------------------|
| Baseline Disease Characteristics | | |
| Characteristic | Thal + Dex (N=103) | Dex alone (N=104) |
| Stage (Durie-Salmon), N (%)¹ | | |
| I | 14 (13.6%) | 17 (16.3%) |
| II | 47 (45.6%) | 44 (42.3%) |
| III | 41 (39.8%) | 43 (41.3%) |
| Immunoglobulin Type, N (%)² | | |
| IgA | 21 (20.4%) | 22 (21.2%) |
| IgG | 63 (61.2%) | 60 (57.7%) |
| IgM | 0 (0.0%) | 1 (1.0%) |
| Biclonal | 0 (0.0%) | 1 (1.0%) |
| Lytic Lesions³ | | |
| None | 28 (27.1%) | 14 (13.5%) |
| 1-3 lesions | 24 (23.3%) | 19 (18.3%) |
| >3 lesions | 34 (33.0%) | 41 (39.4%) |
| Serum Light Chain⁴ | | |
| Kappa | 59 (57.3%) | 53 (51.0%) |
| Lambda | 28 (27.2%) | 40 (38.5%) |

283
284
285
286
287

¹Missing information for 1 patient in Thal + Dex arm
²Missing information for 19 patients in Thal + Dex arm and 20 patients in Dex alone arm
³Missing information for 17 patients in Thal + Dex arm and 30 patients in Dex alone arm
⁴Missing information for 16 patients in Thal + Dex arm and 11 patients in Dex alone arm

288 Response rate was the primary endpoint. Response rates based on serum or urine
289 paraprotein measurements were significantly higher in the combination arm (51.5 %
290 compared with 35.6 % for dexamethasone alone).

291 **Erythema Nodosum Leprosum (ENL)**

292 The primary data demonstrating the efficacy of thalidomide in the treatment of the
 293 cutaneous manifestations of moderate to severe ENL are derived from the published
 294 medical literature and from a retrospective study of 102 patients treated by the U.S.
 295 Public Health Service.

296 Two double-blind, randomized, controlled trials reported the dermatologic response to a
 297 7-day course of 100 mg thalidomide (four times daily) or control. Dosage was lower for
 298 patients under 50 kg in weight.

299

| Table 4 | | | | |
|---|------------------------|-------------------------------|-----------------------------|----------------|
| Double-Blind, Controlled Clinical Trials of Thalidomide in Patients with ENL: Cutaneous Response | | | | |
| Reference | No. of Patients | No. Treatment Courses* | Percent Responding** | |
| Iyer <i>et al.</i> ⁻¹⁰ Bull World Health Organization 1971;45:719 | 92 | 204 | Thalidomide 75% | Aspirin 25% |
| Sheskin <i>et al.</i> ⁻¹¹ Int J Lep 1969;37:135 | 52 | 173 | Thalidomide 66% | Placebo 10% |

300

*In patients with cutaneous lesions

301

**Iyer: Complete response or lesions absent

302

**Sheskin: Complete improvement + “striking” improvement (i.e., >50% improvement)

303 Waters¹² reported the results of two studies, both double-blind, randomized, placebo-
 304 controlled, crossover trials in a total of 10 hospitalized, steroid-dependent patients with
 305 chronic ENL treated with 100 mg thalidomide or placebo (three times daily). All
 306 patients also received dapsone. The primary endpoint was reduction in weekly steroid
 307 dosage.

308

| Table 5 | | | | |
|--|------------------------------|------------------------|--------------------------|----------------|
| Double Blind, Controlled Trial of Thalidomide in Patients with ENL: Reduction in Steroid Dosage | | | | |
| Reference | Duration of Treatment | No. of Patients | Number Responding | |
| | | | Thalidomide | Placebo |
| Waters ¹² | 4 weeks | 9 | 4/5 | 0/4 |
| Lep Rev 1971;42:26 | 6 weeks (crossover) | 8 | 8/8 | 1/8 |

309 Data on the efficacy of thalidomide in prevention of ENL relapse were derived from a
 310 retrospective evaluation of 102 patients treated under the auspices of the U.S. Public
 311 Health Service. A subset of patients with ENL controlled on thalidomide demonstrated
 312 repeated relapse upon drug withdrawal and remission with reinstatement of therapy.

313 Twenty U.S. patients between the ages of 11 and 17 years were treated with
 314 thalidomide, generally at 100 mg daily. Response rates and safety profiles were similar
 315 to that observed in the adult population.

316 Thirty-two other published studies containing over 1600 patients consistently report
 317 generally successful treatment of the cutaneous manifestations of moderate to severe
 318 ENL with thalidomide.

319 **INDICATIONS AND USAGE**320 Multiple Myeloma

321 THALOMID[®] (thalidomide) in combination with dexamethasone is indicated for the
322 treatment of patients with newly diagnosed multiple myeloma.

323 The effectiveness of THALOMID[®] is based on response rates (see **CLINICAL**
324 **STUDIES section**). There are no controlled trials demonstrating a clinical benefit, such
325 as an improvement in survival.

326 Erythema Nodosum Leprosum

327 THALOMID[®] (thalidomide) is indicated for the acute treatment of the cutaneous
328 manifestations of moderate to severe erythema nodosum leprosum (ENL).

329 THALOMID[®] (thalidomide) is not indicated as monotherapy for such ENL treatment in
330 the presence of moderate to severe neuritis.

331 THALOMID[®] (thalidomide) is also indicated as maintenance therapy for prevention
332 and suppression of the cutaneous manifestations of ENL recurrence.

333 **CONTRAINDICATIONS (See BOXED WARNINGS.)**334 **Pregnancy: Category X**

335 Due to its known human teratogenicity, even following a single dose, thalidomide is
336 contraindicated in pregnant women and women capable of becoming pregnant. (See
337 **BOXED WARNINGS**.) When there is no alternative treatment, women of childbearing
338 potential may be treated with thalidomide provided adequate precautions are taken to
339 avoid pregnancy. Women must commit either to abstain continuously from heterosexual
340 sexual contact or to use two methods of reliable birth control, including at least one
341 highly effective method (e.g., IUD, hormonal contraception, tubal ligation, or partner's
342 vasectomy) and one additional effective method (e.g., latex condom, diaphragm, or
343 cervical cap), beginning 4 weeks prior to initiating treatment with thalidomide, during
344 therapy with thalidomide, and continuing for 4 weeks following discontinuation of
345 thalidomide therapy. If hormonal or IUD contraception is medically contraindicated
346 (see also **PRECAUTIONS: Drug Interactions**), two other effective or highly effective
347 methods may be used.

348 Women of childbearing potential being treated with thalidomide should have a
349 pregnancy test (sensitivity of at least 50 mIU/mL). The test should be performed within
350 the 24 hours prior to beginning thalidomide therapy and then weekly during the first 4
351 weeks of thalidomide therapy, then at 4 week intervals in women with regular menstrual
352 cycles or every 2 weeks in women with irregular menstrual cycles. Pregnancy testing
353 and counseling should be performed if a patient misses her period or if there is any
354 abnormality in menstrual bleeding. If pregnancy occurs during thalidomide treatment,
355 thalidomide must be discontinued immediately. Under these conditions, the patient
356 should be referred to an obstetrician/gynecologist experienced in reproductive toxicity
357 for further evaluation and counseling.

358 Because thalidomide is present in the semen of patients receiving the drug, males
359 receiving thalidomide must always use a latex condom during any sexual contact with

360 women of childbearing potential. The risk to the fetus from the semen of male patients
361 taking thalidomide is unknown.

362 THALOMID[®] (thalidomide) is contraindicated in patients who have demonstrated
363 hypersensitivity to the drug and its components.

364 **WARNINGS (See BOXED WARNINGS.)**

365 **Birth Defects:**

366 Thalidomide can cause severe birth defects in humans. (See **BOXED WARNINGS** and
367 **CONTRAINDICATIONS**.) Patients should be instructed to take thalidomide only as
368 prescribed and not to share their thalidomide with anyone else. Because thalidomide is
369 present in the semen of patients receiving the drug, males receiving thalidomide must
370 always use a latex condom during any sexual contact with women of childbearing
371 potential. The risk to the fetus from the semen of male patients taking thalidomide is
372 unknown.

373 **Thrombotic Events:**

374 The use of Thalomid[®] (thalidomide) in multiple myeloma results in an increased risk of
375 venous thromboembolic events, such as deep venous thrombosis and pulmonary
376 embolus. This risk increases significantly when thalidomide is used in combination
377 with standard chemotherapeutic agents including dexamethasone. In one controlled
378 trial, the rate of venous thromboembolic events was 22.5% in patients receiving
379 thalidomide in combination with dexamethasone compared to 4.9% in patients
380 receiving dexamethasone alone ($p = 0.002$). Patients and physicians are advised to be
381 observant for the signs and symptoms of thromboembolism. Patients should be
382 instructed to seek medical care if they develop symptoms such as shortness of breath,
383 chest pain, or arm or leg swelling. Preliminary data suggest that patients who are
384 appropriate candidates may benefit from concurrent prophylactic anticoagulation or
385 aspirin treatment (See **BOXED WARNINGS**).

386 **Drowsiness and Somnolence:**

387 Thalidomide frequently causes drowsiness and somnolence. Patients should be
388 instructed to avoid situations where drowsiness may be a problem and not to take other
389 medications that may cause drowsiness without adequate medical advice. Patients
390 should be advised as to the possible impairment of mental and/or physical abilities
391 required for the performance of hazardous tasks, such as driving a car or operating other
392 complex or dangerous machinery.

393 **Peripheral Neuropathy:**

394 Thalidomide is known to cause nerve damage that may be permanent. Peripheral
395 neuropathy is a common, potentially severe, side effect of treatment with thalidomide
396 that may be irreversible. Peripheral neuropathy generally occurs following chronic use
397 over a period of months; however, reports following relatively short-term use also exist.
398 The correlation with cumulative dose is unclear. Symptoms may occur some time after
399 thalidomide treatment has been stopped and may resolve slowly or not at all.

400 Few reports of neuropathy have arisen in the treatment of ENL despite long-term
401 thalidomide treatment. However, the inability clinically to differentiate thalidomide
402 neuropathy from the neuropathy often seen in Hansen's disease makes it difficult to
403 determine accurately the incidence of thalidomide-related neuropathy in ENL patients
404 treated with thalidomide.

405 Patients should be examined at monthly intervals for the first 3 months of thalidomide
406 therapy to enable the clinician to detect early signs of neuropathy, which include
407 numbness, tingling or pain in the hands and feet. Patients should be evaluated
408 periodically thereafter during treatment. Patients should be regularly counseled,
409 questioned, and evaluated for signs or symptoms of peripheral neuropathy.
410 Consideration should be given to electrophysiological testing, consisting of
411 measurement of sensory nerve action potential (SNAP) amplitudes at baseline and
412 thereafter every 6 months in an effort to detect asymptomatic neuropathy. If symptoms
413 of drug-induced neuropathy develop, thalidomide should be discontinued immediately
414 to limit further damage, if clinically appropriate. Usually, treatment with thalidomide
415 should only be reinitiated if the neuropathy returns to baseline status. Medications
416 known to be associated with neuropathy should be used with caution in patients
417 receiving thalidomide.

418 **Dizziness and Orthostatic Hypotension:**

419 Patients should also be advised that thalidomide may cause dizziness and orthostatic
420 hypotension and that, therefore, they should sit upright for a few minutes prior to
421 standing up from a recumbent position.

422 **Neutropenia:**

423 Decreased white blood cell counts, including neutropenia, have been reported in
424 association with the clinical use of thalidomide. Treatment should not be initiated with
425 an absolute neutrophil count (ANC) of $<750/\text{mm}^3$. White blood cell count and
426 differential should be monitored on an ongoing basis, especially in patients who may be
427 more prone to neutropenia, such as patients who are HIV-seropositive. If ANC
428 decreases to below $750/\text{mm}^3$ while on treatment, the patient's medication regimen
429 should be re-evaluated and, if the neutropenia persists, consideration should be given to
430 withholding thalidomide if clinically appropriate.

431 **Increased HIV Viral Load:**

432 In a randomized, placebo controlled trial of thalidomide in an HIV-seropositive patient
433 population, plasma HIV RNA levels were found to increase (median change = 0.42
434 \log_{10} copies HIV RNA/mL, $p = 0.04$ compared to placebo).⁷ A similar trend was
435 observed in a second, unpublished study conducted in patients who were HIV-
436 seropositive.¹³ The clinical significance of this increase is unknown. Both studies were
437 conducted prior to availability of highly active antiretroviral therapy. Until the clinical
438 significance of this finding is further understood, in HIV-seropositive patients, viral
439 load should be measured after the first and third months of treatment and every 3
440 months thereafter.

441 **PRECAUTIONS**

442 General:

443 The only type of thalidomide exposure known to result in drug associated birth defects
444 are as a result of direct oral ingestion of thalidomide. Currently no specific data are
445 available regarding the cutaneous absorption or inhalation of thalidomide in women of
446 child-bearing potential and whether these exposures may result in any birth defects.
447 Patients should be instructed to not extensively handle or open THALOMID[®]
448 (thalidomide) Capsules and to maintain storage of capsules in blister packs until
449 ingestion. If there is contact with non-intact thalidomide capsules or the powder
450 contents, the exposed area should be washed with soap and water.

451 Thalidomide has been shown to be present in the serum and semen of patients receiving
452 thalidomide. If healthcare providers or other care givers are exposed to body fluids
453 from patients receiving THALOMID[®] (thalidomide), appropriate precautions should be
454 utilized, such as wearing gloves to prevent the potential cutaneous exposure to
455 THALOMID[®] (thalidomide) or the exposed area should be washed with soap and water.

456 Hypersensitivity:

457 Hypersensitivity to THALOMID[®] (thalidomide) has been reported. Signs and
458 symptoms have included the occurrence of erythematous macular rash, possibly
459 associated with fever, tachycardia, and hypotension, and if severe, may necessitate
460 interruption of therapy. If the reaction recurs when dosing is resumed, THALOMID[®]
461 (thalidomide) should be discontinued.

462 Bradycardia:

463 Bradycardia in association with thalidomide use has been reported. Cases of
464 bradycardia have been reported, some required medical interventions. The clinical
465 significance and underlying etiology of the bradycardia noted in some thalidomide-
466 treated patients are presently unknown.

467 Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis:

468 Serious dermatologic reactions including Stevens-Johnson syndrome and toxic
469 epidermal necrolysis, which may be fatal, have been reported. THALOMID[®]
470 (thalidomide) should be discontinued if a skin rash occurs and only resumed following
471 appropriate clinical evaluation. If the rash is exfoliative, purpuric, or bullous or if
472 Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected, use of
473 THALOMID[®] (thalidomide) should not be resumed.

474 Seizures:

475 Although not reported from pre-marketing controlled clinical trials, seizures, including
476 grand mal convulsions, have been reported during post-approval use of THALOMID[®]
477 (thalidomide) in clinical practice. Because these events are reported voluntarily from a
478 population of unknown size, estimates of frequency cannot be made. Most patients had
479 disorders that may have predisposed them to seizure activity, and it is not currently
480 known whether thalidomide has any epileptogenic influence. During therapy with
481 thalidomide, patients with a history of seizures or with other risk factors for the

482 development of seizures should be monitored closely for clinical changes that could
483 precipitate acute seizure activity.

484 **Information for Patients (See BOXED WARNINGS.)**

485 Patients should be instructed about the potential teratogenicity of thalidomide and the
486 precautions that must be taken to preclude fetal exposure as per the *S.T.E.P.S.*[®] program
487 and boxed warnings in this package insert. Patients should be instructed to take
488 thalidomide only as prescribed in compliance with all of the provisions of the
489 *S.T.E.P.S.*[®] Restricted Distribution Program.

490 Patients should be instructed to not extensively handle or open THALOMID[®]
491 (thalidomide) Capsules and to maintain storage of capsules in blister packs until
492 ingestion.

493 Patients should be instructed not to share medication with anyone else.

494 Patients should be instructed that thalidomide frequently causes drowsiness and
495 somnolence. Patients should be instructed to avoid situations where drowsiness may be
496 a problem and not to take other medications that may cause drowsiness without
497 adequate medical advice. Patients should be advised as to the possible impairment of
498 mental and/or physical abilities required for the performance of hazardous tasks, such as
499 driving a car or operating other complex machinery. Patients should be instructed that
500 thalidomide may potentiate the somnolence caused by alcohol.

501 Patients should be instructed that thalidomide can cause peripheral neuropathies that
502 may be initially signaled by numbness, tingling, or pain or a burning sensation in the
503 feet or hands. Patients should be instructed to report such occurrences to their prescriber
504 immediately.

505 Patients should also be instructed that thalidomide may cause dizziness and orthostatic
506 hypotension and that, therefore, they should sit upright for a few minutes prior to
507 standing up from a recumbent position.

508 Patients should be instructed that they are not permitted to donate blood while taking
509 thalidomide. In addition, male patients should be instructed that they are not permitted
510 to donate sperm while taking thalidomide.

511 Patients should be educated about the signs and symptoms of thromboembolism and
512 instructed to seek medical care if they develop symptoms such as shortness of breath,
513 chest pain, or arm or leg swelling.

514 Laboratory Tests

515 ***Pregnancy Testing:*** (See **BOXED WARNINGS**.) Women of childbearing potential
516 should have a pregnancy test performed (sensitivity of at least 50 mIU/mL). The test
517 should be performed within the 24 hours prior to beginning thalidomide therapy and
518 then weekly during the first 4 weeks of use, then at 4 week intervals in women with
519 regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles.
520 Pregnancy testing and counseling should be performed if a patient misses her period or
521 if there is any abnormality in menstrual bleeding.

522 ***Neutropenia:*** (See **WARNINGS**.)

523 ***Increased HIV Viral Load:*** (See **WARNINGS**.)

524 Drug Interactions

525 Thalidomide has been reported to enhance the sedative activity of barbiturates, alcohol,
526 chlorpromazine, and reserpine.

527 ***Peripheral Neuropathy:*** Medications known to be associated with peripheral
528 neuropathy should be used with caution in patients receiving thalidomide.

529 ***Oral Contraceptives:*** In 10 healthy women, the pharmacokinetic profiles of
530 norethindrone and ethinyl estradiol following administration of a single dose containing
531 1.0 mg of norethindrone acetate and 75 µg of ethinyl estradiol were studied. The results
532 were similar with and without coadministration of thalidomide 200 mg/day to steady-
533 state levels.

534 Important Non-Thalidomide Drug Interactions

535 ***Drugs That Interfere with Hormonal Contraceptives:*** Concomitant use of HIV-
536 protease inhibitors, griseofulvin, modafinil, pencillins, rifampin, rifabutin, phenytoin,
537 carbamazepine, or certain herbal supplements such as St. John's Wort with hormonal
538 contraceptive agents may reduce the effectiveness of the contraception and up to one
539 month after discontinuation of these concomitant therapies. Therefore, women requiring
540 treatment with one or more of these drugs must use two OTHER effective or highly
541 effective methods of contraception or abstain from heterosexual sexual contact while
542 taking thalidomide.

543 Carcinogenesis, Mutagenesis, Impairment of Fertility

544 Two-year carcinogenicity studies were conducted in male and female rats and mice. No
545 compound-related tumorigenic effects were observed at the highest dose levels of 3,000
546 mg/kg/day to male and female mice (38-fold greater than the highest recommended
547 daily human dose of 400 mg based upon body surface area [BSA]), 3,000 mg/kg/day to
548 female rats (75-fold the maximum human dose based upon BSA), and 300 mg/kg/day to
549 male rats (7.5-fold the maximum human dose based upon BSA).

550 Thalidomide was neither mutagenic nor genotoxic in the following assays: the Ames
551 bacterial (*S. typhimurium* and *E. coli*) reverse mutation assay, a Chinese hamster ovary
552 cell (AS52/XPRT) forward mutation assay, and an *in vivo* mouse micronucleus test.

553 Fertility studies were conducted in male and female rabbits; no compound-related
554 effects in mating and fertility indices were observed at any oral thalidomide dose level
555 including the highest of 100 mg/kg/day to female rabbits and 500 mg/kg/day to male
556 rabbits (approximately 5- and 25-fold the maximum human dose, respectively, based
557 upon BSA). Testicular pathological and histopathological effects (classified as slight)
558 were seen in male rabbits at dose levels ≥ 30 mg/kg/day (approximately 1.5-fold the
559 maximum human dose based upon BSA).

560 **Pregnancy**

561 ***Pregnancy Category X (See BOXED WARNING and CONTRAINDICATIONS.)***

562 Because of the known human teratogenicity of thalidomide, thalidomide is
563 contraindicated in women who are or may become pregnant and who are not using the
564 two required types of birth control or who are not continually abstaining from
565 heterosexual sexual contact. If thalidomide is taken during pregnancy, it can cause
566 severe birth defects or death to an unborn baby. Thalidomide should never be used by
567 women who are pregnant or who could become pregnant while taking the drug. Even a
568 single dose [1 capsule (50 mg, 100 mg, or a 200 mg)] taken by a pregnant woman can
569 cause birth defects. If pregnancy does occur during treatment, the drug should be
570 immediately discontinued. Under these conditions, the patient should be referred to an
571 obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and
572 counseling. Any suspected fetal exposure to THALOMID[®] (thalidomide) must be
573 reported to the FDA *via* the MedWatch program at 1-800-FDA-1088 and also to
574 Celgene Corporation.

575 Because thalidomide is present in the semen of patients receiving the drug, males
576 receiving thalidomide must always use a latex condom during any sexual contact with
577 women of childbearing potential. The risk to the fetus from the semen of male patients
578 taking thalidomide is unknown.

579 A pre- and postnatal reproductive toxicity study was conducted in pregnant female
580 rabbits. Compound-related increased abortion incidences and elevated fetotoxicity were
581 observed at the lowest oral dose level of 30 mg/kg/day (approximately 1.5-fold the
582 maximum human dose based upon BSA) and all higher dose levels. Neonatal mortality
583 was elevated at oral dose levels to the lactating female rabbits ≥ 150 mg/kg/day
584 (approximately 7.5-fold the maximum human dose based upon BSA). No delay in
585 postnatal development, including learning and memory functions, were noted at the oral
586 dose level to the lactating female rabbits of 150 mg/kg/day (average thalidomide
587 concentrations in milk ranged from 22 to 36 $\mu\text{g/ml}$).

588 Use in Nursing Mothers

589 It is not known whether thalidomide is excreted in human milk. Because many drugs
590 are excreted in human milk and because of the potential for serious adverse reactions in
591 nursing infants from thalidomide, a decision should be made whether to discontinue
592 nursing or to discontinue the drug, taking into account the importance of the drug to the
593 mother.

594 Pediatric Use

595 Safety and effectiveness in pediatric patients below the age of 12 years have not been
596 established.

597 Geriatric Use

598 Of the total number of subjects in this clinical study of thalidomide and dexamethasone
599 combination, 50% were 65 and over, while 15% were 75 and over. No overall
600 differences in safety and effectiveness were observed between these subjects and
601 younger subjects, and other reported clinical experience has not identified differences in
602 responses between the elderly and younger patients, but greater sensitivity of some
603 older individuals cannot be ruled out.

604 ADVERSE REACTIONS

605 The most serious toxicity associated with thalidomide is its documented human
606 teratogenicity. (See **BOXED WARNINGS** and **CONTRAINDICATIONS**.) The risk
607 of severe birth defects, primarily phocomelia or death to the fetus, is extremely high
608 during the critical period of pregnancy. The critical period is estimated, depending on
609 the source of information, to range from 35 to 50 days after the last menstrual period.
610 The risk of other potentially severe birth defects outside this critical period is unknown,
611 but may be significant. Based on present knowledge, thalidomide must not be used at
612 any time during pregnancy.

613 Because thalidomide is present in the semen of patients receiving the drug, males
614 receiving thalidomide must always use a latex condom during any sexual contact with
615 women of childbearing potential.

616 Thalidomide is associated with drowsiness/somnolence, peripheral neuropathy,
617 dizziness/orthostatic hypotension, neutropenia, and HIV viral load increase. (See
618 **WARNINGS**.)

619 Hypersensitivity to THALOMID[®] (thalidomide) and bradycardia in patients treated
620 with thalidomide have been reported. (See **PRECAUTIONS**.)

621 Somnolence, dizziness, and rash are the most commonly observed adverse events
622 associated with the use of thalidomide. Thalidomide has been studied in controlled and
623 uncontrolled clinical trials in patients with multiple myeloma and ENL and in people
624 who are HIV-seropositive. In addition, thalidomide has been administered
625 investigationally for more than 20 years in numerous indications. Adverse event profiles
626 from these uses are summarized in the sections that follow.

627 Other Adverse Events

628 Due to the nature of the longitudinal data that form the basis of this product’s safety
 629 evaluation, no determination has been made of the causal relationship between the
 630 reported adverse events listed below and thalidomide. These lists are of various adverse
 631 events noted by investigators in patients to whom they had administered thalidomide
 632 under various conditions. The use of thalidomide may not limit disease progression
 633 and/or death.

634 **Adverse events in Multiple Myeloma Controlled Clinical Trial**

635 The safety analysis was conducted on 204 patients who received study drug in the
 636 randomized trial. Table 6 lists the most common treatment – emergent signs and
 637 symptoms (occurring at ≥ 10%) that were observed. The most frequently reported
 638 adverse events were constipation, sensory neuropathy, confusion, hypocalcemia, edema,
 639 dyspnea, thrombosis/embolism, and rash/desquamation (occurring in ≥20% of patients
 640 and with a frequency of ≥10% in patients treated with Thalomid[®]/dexamethasone
 641 compared with dexamethasone alone).

642 Twenty-three percent of patients (47/204) discontinued due to adverse events; thirty
 643 percent (31/102) from the Thalomid[®]/dexamethasone arm and sixteen percent (16/102)
 644 from the dexamethasone alone arm.

645 **Table 6**
 646 **Treatment-Emergent Adverse Events in ≥ 10% of All Patients**
 647 **Adverse Event (Safety Population; N=204)**

| Organ System Class/Preferred Term | Thal + Dex (N=102) | | | Dex Alone (N=102) | | |
|-----------------------------------|--------------------|------------------------|------------------------|--------------------|------------------------|------------------------|
| | All Events [n,(%)] | Grade 3 Events [n,(%)] | Grade 4 Events [n,(%)] | All Events [n,(%)] | Grade 3 Events [n,(%)] | Grade 4 Events [n,(%)] |
| Metabolic/Laboratory | 97 (95.1) | 30 (29.4) | 15 (14.7) | 96 (94.1) | 28 (27.5) | 6 (5.9) |
| Hyperglycemia | 74 (72.5) | 12 (11.8) | 4 (3.9) | 81 (79.4) | 17 (16.7) | 2 (2.0) |
| Hypocalcemia | 73 (71.6) | 9 (8.8) | 6 (5.9) | 60 (58.8) | 4 (3.9) | 1 (1.0) |
| Hyponatremia | 44 (43.1) | 11 (10.8) | 2 (2.0) | 49 (48.0) | 13 (12.7) | 2 (2.0) |
| Hypokalemia | 23 (22.5) | 4 (3.9) | 1 (1.0) | 23 (22.5) | 0 (0.0) | 1 (1.0) |
| Hyperkalemia | 19 (18.6) | 1 (1.0) | 2 (2.0) | 20 (19.6) | 2 (2.0) | 0 (0.0) |
| Neurology | 92 (90.2) | 27 (26.5) | 5 (4.9) | 76 (74.5) | 15 (14.7) | 4 (3.9) |
| Neuropathy-sensory | 55 (53.9) | 3 (2.9) | 1 (1.0) | 28 (27.5) | 1 (1.0) | 0 (0.0) |
| Confusion | 29 (28.4) | 6 (5.9) | 3 (2.9) | 12 (11.8) | 2 (2.0) | 3 (2.9) |
| Anxiety / agitation | 26 (25.5) | 1 (1.0) | 0 (0.0) | 14 (13.7) | 3 (2.9) | 0 (0.0) |
| Tremor | 26 (25.5) | 1 (1.0) | 0 (0.0) | 6 (5.9) | 0 (0.0) | 0 (0.0) |
| Insomnia | 23 (22.5) | 0 (0.0) | 0 (0.0) | 48 (47.1) | 5 (4.9) | 0 (0.0) |
| Depression | 22 (21.6) | 2 (2.0) | 0 (0.0) | 24 (23.5) | 1 (1.0) | 0 (0.0) |
| Neuropathy-motor | 22 (21.6) | 7 (6.9) | 1 (1.0) | 16 (15.7) | 5 (4.9) | 1 (1.0) |
| Dizziness / lightheadedness | 20 (19.6) | 1 (1.0) | 0 (0.0) | 14 (13.7) | 0 (0.0) | 0 (0.0) |
| Constitutional Symptoms | 91 (89.2) | 17 (16.7) | 3 (2.9) | 84 (82.4) | 15 (14.7) | 2 (2.0) |
| Fatigue | 81 (79.4) | 14 (13.7) | 3 (2.9) | 72 (70.6) | 12 (11.8) | 2 (2.0) |
| Fever | 24 (23.5) | 1 (1.0) | 0 (0.0) | 20 (19.6) | 3 (2.9) | 0 (0.0) |
| Weight loss | 23 (22.5) | 1 (1.0) | 0 (0.0) | 21 (20.6) | 2 (2.0) | 0 (0.0) |
| Weight gain | 22 (21.6) | 1 (1.0) | 0 (0.0) | 13 (12.7) | 0 (0.0) | 0 (0.0) |
| Blood/Bone Marrow | 88 (86.3) | 25 (24.5) | 9 (8.8) | 96 (94.1) | 10 (9.8) | 10 (9.8) |
| Hemoglobin (decreased) | 79 (77.5) | 13 (12.7) | 3 (2.9) | 88 (86.3) | 5 (4.9) | 1 (1.0) |
| Leukocytes (decreased) | 36 (35.3) | 6 (5.9) | 1 (1.0) | 30 (29.4) | 1 (1.0) | 2 (2.0) |
| Neutrophils (decreased) | 32 (31.4) | 8 (7.8) | 5 (4.9) | 24 (23.5) | 3 (2.9) | 8 (7.8) |
| Platelets (decreased) | 24 (23.5) | 2 (2.0) | 2 (2.0) | 34 (33.3) | 3 (2.9) | 0 (0.0) |
| Gastrointestinal | 83 (81.4) | 19 (18.6) | 3 (2.9) | 70 (68.6) | 8 (7.8) | 0 (0.0) |

| | | | | | | |
|---|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-----------------------|
| <u>Constipation</u> | <u>56 (54.9)</u> | <u>8 (7.8)</u> | <u>0 (0.0)</u> | <u>29 (28.4)</u> | <u>1 (1.0)</u> | <u>0 (0.0)</u> |
| <u>Anorexia</u> | <u>29 (28.4)</u> | <u>4 (3.9)</u> | <u>0 (0.0)</u> | <u>25 (24.5)</u> | <u>2 (2.0)</u> | <u>0 (0.0)</u> |
| <u>Nausea</u> | <u>29 (28.4)</u> | <u>5 (4.9)</u> | <u>0 (0.0)</u> | <u>23 (22.5)</u> | <u>1 (1.0)</u> | <u>0 (0.0)</u> |
| <u>Vomiting</u> | <u>12 (11.8)</u> | <u>2 (2.0)</u> | <u>0 (0.0)</u> | <u>12 (11.8)</u> | <u>1 (1.0)</u> | <u>0 (0.0)</u> |
| <u>Diarrhea</u> | <u>12 (11.8)</u> | <u>1 (1.0)</u> | <u>0 (0.0)</u> | <u>17 (16.7)</u> | <u>3 (2.9)</u> | <u>0 (0.0)</u> |
| <u>Dyspepsia</u> | <u>8 (7.8)</u> | <u>1 (1.0)</u> | <u>0 (0.0)</u> | <u>19 (18.6)</u> | <u>1 (1.0)</u> | <u>0 (0.0)</u> |
| <u>Cardiovascular</u> | <u>70 (68.6)</u> | <u>24 (23.5)</u> | <u>14 (13.7)</u> | <u>60 (58.8)</u> | <u>17 (16.7)</u> | <u>5 (4.9)</u> |
| <u>Edema</u> | <u>58 (56.9)</u> | <u>6 (5.9)</u> | <u>0 (0.0)</u> | <u>47 (46.1)</u> | <u>4 (3.9)</u> | <u>0 (0.0)</u> |
| <u>Thrombosis/embolism</u> | <u>23 (22.5)</u> | <u>13 (12.7)</u> | <u>9 (8.8)</u> | <u>5 (4.9)</u> | <u>3 (2.9)</u> | <u>2 (2.0)</u> |
| <u>Hypotension</u> | <u>16 (15.7)</u> | <u>7 (6.9)</u> | <u>2 (2.0)</u> | <u>15 (14.7)</u> | <u>2 (2.0)</u> | <u>3 (2.9)</u> |
| <u>Hypertension</u> | <u>11 (10.8)</u> | <u>1 (1.0)</u> | <u>0 (0.0)</u> | <u>12 (11.8)</u> | <u>9 (8.8)</u> | <u>0 (0.0)</u> |
| <u>Pain</u> | <u>64 (62.7)</u> | <u>8 (7.8)</u> | <u>2 (2.0)</u> | <u>66 (64.7)</u> | <u>15 (14.7)</u> | <u>0 (0.0)</u> |
| <u>Bone pain</u> | <u>31 (30.4)</u> | <u>3 (2.9)</u> | <u>2 (2.0)</u> | <u>37 (36.3)</u> | <u>11 (10.8)</u> | <u>0 (0.0)</u> |
| <u>Pain-other</u> | <u>25 (24.5)</u> | <u>4 (3.9)</u> | <u>0 (0.0)</u> | <u>26 (25.5)</u> | <u>3 (2.9)</u> | <u>0 (0.0)</u> |
| <u>Headache</u> | <u>20 (19.6)</u> | <u>3 (2.9)</u> | <u>0 (0.0)</u> | <u>23 (22.5)</u> | <u>0 (0.0)</u> | <u>0 (0.0)</u> |
| <u>Myalgia</u> | <u>17 (16.7)</u> | <u>0 (0.0)</u> | <u>0 (0.0)</u> | <u>14 (13.7)</u> | <u>1 (1.0)</u> | <u>0 (0.0)</u> |
| <u>Arthralgia</u> | <u>13 (12.7)</u> | <u>0 (0.0)</u> | <u>0 (0.0)</u> | <u>10 (9.8)</u> | <u>2 (2.0)</u> | <u>0 (0.0)</u> |
| <u>Pulmonary</u> | <u>52 (51.0)</u> | <u>15 (14.7)</u> | <u>6 (5.9)</u> | <u>51 (50.0)</u> | <u>15 (14.7)</u> | <u>5 (4.9)</u> |
| <u>Dyspnea</u> | <u>43 (42.2)</u> | <u>10 (9.8)</u> | <u>3 (2.9)</u> | <u>32 (31.4)</u> | <u>12 (11.8)</u> | <u>4 (3.9)</u> |
| <u>Cough</u> | <u>15 (14.7)</u> | <u>0 (0.0)</u> | <u>0 (0.0)</u> | <u>19 (18.6)</u> | <u>0 (0.0)</u> | <u>0 (0.0)</u> |
| <u>Dermatology/Skin</u> | <u>48 (47.1)</u> | <u>5 (4.9)</u> | <u>1 (1.0)</u> | <u>35 (34.3)</u> | <u>2 (2.0)</u> | <u>0 (0.0)</u> |
| <u>Rash/desquamation</u> | <u>31 (30.4)</u> | <u>4 (3.9)</u> | <u>0 (0.0)</u> | <u>18 (17.6)</u> | <u>2 (2.0)</u> | <u>0 (0.0)</u> |
| <u>Dry skin</u> | <u>21 (20.6)</u> | <u>0 (0.0)</u> | <u>0 (0.0)</u> | <u>11 (10.8)</u> | <u>0 (0.0)</u> | <u>0 (0.0)</u> |
| <u>Hepatic</u> | <u>47 (46.1)</u> | <u>5 (4.9)</u> | <u>2 (2.0)</u> | <u>45 (44.1)</u> | <u>3 (2.9)</u> | <u>1 (1.0)</u> |
| <u>Alkaline phosphatase (increased)</u> | <u>27 (26.5)</u> | <u>0 (0.0)</u> | <u>0 (0.0)</u> | <u>29 (28.4)</u> | <u>1 (1.0)</u> | <u>0 (0.0)</u> |
| <u>SGOT (increased)</u> | <u>25 (24.5)</u> | <u>1 (1.0)</u> | <u>1 (1.0)</u> | <u>24 (23.5)</u> | <u>1 (1.0)</u> | <u>1 (1.0)</u> |
| <u>Bilirubin (increased)</u> | <u>14 (13.7)</u> | <u>1 (1.0)</u> | <u>1 (1.0)</u> | <u>10 (9.8)</u> | <u>1 (1.0)</u> | <u>1 (1.0)</u> |
| <u>Renal/Genitourinary</u> | <u>43 (42.2)</u> | <u>3 (2.9)</u> | <u>3 (2.9)</u> | <u>49 (48.0)</u> | <u>4 (3.9)</u> | <u>3 (2.9)</u> |
| <u>Creatinine</u> | <u>36 (35.3)</u> | <u>1 (1.0)</u> | <u>1 (1.0)</u> | <u>43 (42.2)</u> | <u>2 (2.0)</u> | <u>2 (2.0)</u> |
| <u>Musculoskeletal</u> | <u>42 (41.2)</u> | <u>8 (7.8)</u> | <u>2 (2.0)</u> | <u>41 (40.2)</u> | <u>11 (10.8)</u> | <u>3 (2.9)</u> |
| <u>Muscle weakness</u> | <u>41 (40.2)</u> | <u>6 (5.9)</u> | <u>1 (1.0)</u> | <u>38 (37.3)</u> | <u>10 (9.8)</u> | <u>3 (2.9)</u> |
| <u>Infection/Febrile</u> | <u>23 (22.5)</u> | <u>5 (4.9)</u> | <u>2 (2.0)</u> | <u>28 (27.5)</u> | <u>6 (5.9)</u> | <u>6 (5.9)</u> |
| <u>Neutropenia</u> | <u>23 (22.5)</u> | <u>5 (4.9)</u> | <u>2 (2.0)</u> | <u>28 (27.5)</u> | <u>6 (5.9)</u> | <u>6 (5.9)</u> |
| <u>Infection without neutropenia</u> | <u>19 (17.6)</u> | <u>4 (3.9)</u> | <u>1 (1.0)</u> | <u>18 (17.6)</u> | <u>4 (3.9)</u> | <u>2 (2.0)</u> |

648 **Incidence in ENL Controlled Clinical Trials**

649 Table 7 lists treatment-emergent signs and symptoms that occurred in THALOMID[®]
650 (thalidomide)-treated patients in controlled clinical trials in ENL. Doses ranged from 50
651 to 300 mg/day. All adverse events were mild to moderate in severity, and none resulted
652 in discontinuation. Table 7 also lists treatment-emergent adverse events that occurred in
653 at least three of the THALOMID[®] (thalidomide)-treated HIV-seropositive patients who
654 participated in an 8-week, placebo-controlled clinical trial. Events that were more
655 frequent in the placebo-treated group are not included. (See **WARNINGS**,
656 **PRECAUTIONS**, and **Drug Interactions**.)

| Table 7 | | | | |
|---|---|---|------------------------------|-------------------|
| Summary of Adverse Events (AEs) | | | | |
| Reported in Celgene-sponsored Controlled Clinical Trials | | | | |
| Body System/Adverse Event | All AEs Reported in ENL Patients | AEs Reported in ≥3 HIV-seropositive Patients | | |
| | 50 to 300 mg/day (N=24) | Thalidomide | | Placebo |
| | | 100 mg/day (N=36) | 200 mg/day (N=32) | (N=35) |
| Body as a Whole | 16 (66.7%) | 18 (50.0%) | 19 (59.4%) | 13 (37.1%) |
| Abdominal pain | 1 (4.2%) | 1 (2.8%) | 1 (3.1%) | 4 (11.4%) |
| Accidental injury | 1 (4.2%) | 2 (5.6%) | 0 | 1 (2.9%) |
| Asthenia | 2 (8.3%) | 2 (5.6%) | 7 (21.9%) | 1 (2.9%) |
| Back pain | 1 (4.2%) | 2 (5.6%) | 0 | 0 |
| Chills | 1 (4.2%) | 0 | 3 (9.4%) | 4 (11.4%) |
| Facial edema | 1 (4.2%) | 0 | 0 | 0 |
| Fever | 0 | 7 (19.4%) | 7 (21.9%) | 6 (17.1%) |
| Headache | 3 (12.5%) | 6 (16.7%) | 6 (18.7%) | 4 (11.4%) |
| Infection | 0 | 3 (8.3%) | 2 (6.3%) | 1 (2.9%) |
| Malaise | 2 (8.3%) | 0 | 0 | 0 |
| Neck pain | 1 (4.2%) | 0 | 0 | 0 |
| Neck rigidity | 1 (4.2%) | 0 | 0 | 0 |
| Pain | 2 (8.3%) | 0 | 1 (3.1%) | 2 (5.7%) |
| Digestive System | 5 (20.8%) | 16 (44.4%) | 16 (50.0%) | 15 (42.9%) |
| Anorexia | 0 | 1 (2.8%) | 3 (9.4%) | 2 (5.7%) |
| Constipation | 1 (4.2%) | 1 (2.8%) | 3 (9.4%) | 0 |
| Diarrhea | 1 (4.2%) | 4 (11.1%) | 6 (18.7%) | 6 (17.1%) |
| Dry mouth | 0 | 3 (8.3%) | 3 (9.4%) | 2 (5.7%) |
| Flatulence | 0 | 3 (8.3%) | 0 | 2 (5.7%) |
| Liver function tests multiple abnormalities | 0 | 0 | 3 (9.4%) | 0 |
| Nausea | 1 (4.2%) | 0 | 4 (12.5%) | 1 (2.9%) |
| Oral moniliasis | 1 (4.2%) | 4 (11.1%) | 2 (6.3%) | 0 |
| Tooth pain | 1 (4.2%) | 0 | 0 | 0 |
| Hemic and Lymphatic | 0 | 8 (22.2%) | 13 (40.6%) | 10 (28.6%) |
| Anemia | 0 | 2 (5.6%) | 4 (12.5%) | 3 (8.6%) |
| Leukopenia | 0 | 6 (16.7%) | 3 (9.4%) | 3 (8.6%) |
| Lymphadenopathy | 0 | 2 (5.6%) | 4 (12.5%) | 3 (8.6%) |
| Metabolic and Endocrine Disorders | 1 (4.2%) | 8 (22.2%) | 12 (37.5%) | 8 (22.9%) |
| Edema peripheral | 1 (4.2%) | 3 (8.3%) | 1 (3.1%) | 0 |
| Hyperlipemia | 0 | 2 (5.6%) | 3 (9.4%) | 1 (2.9%) |
| SGOT increased | 0 | 1 (2.8%) | 4 (12.5%) | 2 (5.7%) |
| Nervous System | 13 (54.2%) | 19 (52.8%) | 18 (56.3%) | 12 (34.3%) |
| Agitation | 0 | 0 | 3 (9.4%) | 0 |
| Dizziness | 1 (4.2%) | 7 (19.4%) | 6 (18.7%) | 0 |
| Insomnia | 0 | 0 | 3 (9.4%) | 2 (5.7%) |
| Nervousness | 0 | 1 (2.8%) | 3 (9.4%) | 0 |
| Neuropathy | 0 | 3 (8.3%) | 0 | 0 |
| Paresthesia | 0 | 2 (5.6%) | 5 (15.6%) | 4 (11.4%) |
| Somnolence | 9 (37.5%) | 13 (36.1%) | 12 (37.5%) | 4 (11.4%) |
| Tremor | 1 (4.2%) | 0 | 0 | 0 |
| Vertigo | 2 (8.3%) | 0 | 0 | 0 |
| Respiratory System | 3 (12.5%) | 9 (25.0%) | 6 (18.7%) | 9 (25.7%) |
| Pharyngitis | 1 (4.2%) | 3 (8.3%) | 2 (6.3%) | 2 (5.7%) |
| Rhinitis | 1 (4.2%) | 0 | 0 | 4 (11.4%) |
| Sinusitis | 1 (4.2%) | 3 (8.3%) | 1 (3.1%) | 2 (5.7%) |
| Skin and Appendages | 10 (41.7%) | 17 (47.2%) | 18 (56.3%) | 19 (54.3%) |
| Acne | 0 | 4 (11.1%) | 1 (3.1%) | 0 |
| Dermatitis fungal | 1 (4.2%) | 2 (5.6%) | 3 (9.4%) | 0 |
| Nail disorder | 1 (4.2%) | 0 | 1 (3.1%) | 0 |
| Pruritus | 2 (8.3%) | 1 (2.8%) | 2 (6.3%) | 2 (5.7%) |
| Rash | 5 (20.8%) | 9 (25.0%) | 8 (25.0%) | 11 (31.4%) |
| Rash maculo-papular | 1 (4.2%) | 6 (16.7%) | 6 (18.7%) | 2 (5.7%) |
| Sweating | 0 | 0 | 4 (12.5%) | 4 (11.4%) |
| Urogenital System | 2 (8.3%) | 6 (16.7%) | 2 (6.3%) | 4 (11.4%) |
| Albuminuria | 0 | 3 (8.3%) | 1 (3.1%) | 2 (5.7%) |
| Hematuria | 0 | 4 (11.1%) | 0 | 1 (2.9%) |
| Impotence | 2 (8.3%) | 1 (2.8%) | 0 | 0 |

658 **Other Adverse Events Observed in ENL Patients**

659 Thalidomide in doses up to 400 mg/day has been administered investigationally in the
660 United States over a 19-year period in 1465 patients with ENL. The published literature
661 describes the treatment of an additional 1678 patients. To provide a meaningful estimate
662 of the proportion of the individuals having adverse events, similar types of events were
663 grouped into a smaller number of standardized categories using a modified COSTART
664 dictionary/terminology. These categories are used in the listing below. All reported
665 events are included except those already listed in the previous table. Due to the fact that
666 these data were collected from uncontrolled studies, the incidence rate cannot be
667 determined. As mentioned previously, **no causal relationship between thalidomide
668 and these events can be conclusively determined at this time.** These are reports of all
669 adverse events noted by investigators in patients to whom they had administered
670 thalidomide.

671 **Body as a Whole:** Abdomen enlarged, fever, photosensitivity, upper extremity pain.

672 **Cardiovascular System:** Bradycardia, hypertension, hypotension, peripheral vascular
673 disorder, tachycardia, vasodilation.

674 **Digestive System:** Anorexia, appetite increase/weight gain, dry mouth, dyspepsia,
675 enlarged liver, eructation, flatulence, increased liver function tests, intestinal
676 obstruction, vomiting.

677 **Hemic and Lymphatic:** ESR decrease, eosinophilia, granulocytopenia, hypochromic
678 anemia, leukemia, leukocytosis, leukopenia, MCV elevated, RBC abnormal, spleen
679 palpable, thrombocytopenia.

680 **Metabolic and Endocrine:** ADH inappropriate, amyloidosis, bilirubinemia, BUN
681 increased, creatinine increased, cyanosis, diabetes, edema, electrolyte abnormalities,
682 hyperglycemia, hyperkalemia, hyperuricemia, hypocalcemia, hypoproteinemia, LDH
683 increased, phosphorus decreased, SGPT increased.

684 **Muscular Skeletal:** Arthritis, bone tenderness, hypertonia, joint disorder, leg cramps,
685 myalgia, myasthenia, periosteal disorder.

686 **Nervous System:** Abnormal thinking, agitation, amnesia, anxiety, causalgia, circumoral
687 paresthesia, confusion, depression, euphoria, hyperesthesia, insomnia, nervousness,
688 neuralgia, neuritis, neuropathy, paresthesia, peripheral neuritis, psychosis.

689 **Respiratory System:** Cough, emphysema, epistaxis, pulmonary embolus, rales, upper
690 respiratory infection, voice alteration.

691 **Skin and Appendages:** Acne, alopecia, dry skin, eczematous rash, exfoliative
692 dermatitis, ichthyosis, perifollicular thickening, skin necrosis, seborrhea, sweating,
693 urticaria, vesiculobullous rash.

694 **Special Senses:** Amblyopia, deafness, dry eye, eye pain, tinnitus.

695 **Urogenital:** Decreased creatinine clearance, hematuria, orchitis, proteinuria, pyuria,
696 urinary frequency.

697 **Other Adverse Events Observed in HIV-seropositive Patients**

698 In addition to controlled clinical trials, THALOMID[®] (thalidomide) has been used in
 699 uncontrolled studies in 145 patients. Less frequent adverse events that have been
 700 reported in these HIV-seropositive patients treated with THALOMID[®] (thalidomide)
 701 were grouped into a smaller number of standardized categories using modified
 702 COSTART dictionary/terminology and these categories are used in the listing below.
 703 Adverse events that have already been included in the tables and narrative above, or that
 704 are too general to be informative are not listed.

705 **Body as a Whole:** Ascites, AIDS, allergic reaction, cellulitis, chest pain, chills and
 706 fever, cyst, decreased CD4 count, facial edema, flu syndrome, hernia, thyroid hormone
 707 level altered, moniliasis, photosensitivity reaction, sarcoma, sepsis, viral infection.

708 **Cardiovascular System:** Angina pectoris, arrhythmia, atrial fibrillation, bradycardia,
 709 cerebral ischemia, cerebrovascular accident, congestive heart failure, deep
 710 thrombophlebitis, heart arrest, heart failure, hypertension, hypotension, murmur,
 711 myocardial infarct, palpitation, pericarditis, peripheral vascular disorder, postural
 712 hypotension, syncope, tachycardia, thrombophlebitis, thrombosis.

713 **Digestive System:** Cholangitis, cholestatic jaundice, colitis, dyspepsia, dysphagia,
 714 esophagitis, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, gum
 715 disorder, hepatitis, pancreatitis, parotid gland enlargement, periodontitis, stomatitis,
 716 tongue discoloration, tooth disorder.

717 **Hemic and Lymphatic:** Aplastic anemia, macrocytic anemia, megaloblastic anemia,
 718 microcytic anemia.

719 **Metabolic and Endocrine:** Avitaminosis, bilirubinemia, dehydration,
 720 hypercholesteremia, hypoglycemia, increased alkaline phosphatase, increased lipase,
 721 increased serum creatinine, peripheral edema.

722 **Muscular Skeletal:** Myalgia, myasthenia.

723 **Nervous System:** Abnormal gait, ataxia, decreased libido, decreased reflexes, dementia,
 724 dysesthesia, dyskinesia, emotional lability, hostility, hypalgesia, hyperkinesia,
 725 incoordination, meningitis, neurologic disorder, tremor, vertigo.

726 **Respiratory System:** Apnea, bronchitis, lung disorder, lung edema, pneumonia
 727 (including *Pneumocystis carinii* pneumonia), rhinitis.

728 **Skin and Appendages:** Angioedema, benign skin neoplasm, eczema, herpes simplex,
 729 incomplete Stevens-Johnson syndrome, nail disorder, pruritus, psoriasis, skin
 730 discoloration, skin disorder.

731 **Special Senses:** Conjunctivitis, eye disorder, lacrimation disorder, retinitis, taste
 732 perversion.

733 **Other Adverse Events Observed in Post-Marketing Use**

734 **Cardiovascular System:** Cardiac arrhythmias including atrial fibrillation, bradycardia,
 735 tachycardia, sick sinus syndrome and EKG abnormalities.

736 **Digestive System:** Intestinal perforation.

737 **Metabolic and Endocrine:** Electrolyte imbalance including hypercalcemia or
 738 hypocalcemia, hyperkalemia and hypokalemia, hyponatremia, hypothyroidism, and
 739 increased alkaline phosphatase, tumor lysis syndrome.

740 **Nervous System:** Changes in mental status or mood including depression and suicide
 741 attempts, disturbances in consciousness including lethargy, syncope, loss of
 742 consciousness or stupor, seizures including grand mal convulsions and status epilepticus.

743 **Skin and Appendages:** Erythema multiforme.

744 **Hemic and Lymphatic:** Decreased white blood cell counts including neutropenia and
 745 febrile neutropenia, changes in prothrombin time.

746 **Respiratory System:** Pleural effusion.

747 **Other Adverse Events in the Published Literature or Reported from Other**
 748 **Sources**

749 The following additional events have been identified either in the published literature or
 750 from spontaneous reports from other sources: acute renal failure, amenorrhea, aphthous
 751 stomatitis, bile duct obstruction, carpal tunnel, chronic myelogenous leukemia, diplopia,
 752 dysesthesia, dyspnea, enuresis, erythema nodosum, erythroleukemia, foot drop,
 753 galactorrhea, gynecomastia, hangover effect, hypomagnesemia, hypothyroidism,
 754 lymphedema, lymphopenia, metrorrhagia, migraine, myxedema, nodular sclerosing
 755 Hodgkin's disease, nystagmus, oliguria, pancytopenia, petechiae, purpura, Raynaud's
 756 syndrome, stomach ulcer, and suicide attempt.

757 **DRUG ABUSE AND DEPENDENCE**

758 Physical and psychological dependence has not been reported in patients taking
 759 thalidomide. However, as with other tranquilizers/hypnotics, thalidomide too has been
 760 reported to create in patients habituation to its soporific effects.

761 **OVERDOSAGE**

762 There have been three cases of overdose reported, all attempted suicides. There have
 763 been no reported fatalities in doses of up to 14.4 grams, and all patients recovered
 764 without reported sequelae.

765 **DOSAGE AND ADMINISTRATION**

766 **THALOMID[®] (thalidomide) MUST ONLY BE ADMINISTERED IN**
 767 **COMPLIANCE WITH ALL OF THE TERMS OUTLINED IN THE S.T.E.P.S.[®]**
 768 **PROGRAM. THALOMID[®] (thalidomide) MAY ONLY BE PRESCRIBED BY**
 769 **PRESCRIBERS REGISTERED WITH THE S.T.E.P.S.[®] PROGRAM AND MAY**
 770 **ONLY BE DISPENSED BY PHARMACISTS REGISTERED WITH THE**
 771 **S.T.E.P.S.[®] PROGRAM.**

772 **Drug prescribing to women of childbearing potential should be contingent upon**
 773 **initial and continued confirmed negative results of pregnancy testing.**

774 Multiple Myeloma

775 THALOMID[®] (thalidomide) is administered in combination with dexamethasone in 28-
776 day treatment cycles. The dose of THALOMID[®] is 200 mg administered orally once
777 daily with water, preferably at bedtime and at least 1-hour after the evening meal. The
778 dose of dexamethasone is 40 mg daily administered orally on days 1-4, 9-12, and 17-20
779 every 28 days.

780 Patients who develop side effects such as constipation, oversedation, or peripheral
781 neuropathy may benefit by either temporarily discontinuing the drug or continuing at a
782 lower dose. With the abatement of these side effects, the drug may be started at a lower
783 dose or at the previous dose based on clinical judgment.

784 Erythema Nodosum Leprosum

785 For an episode of cutaneous ENL, THALOMID[®] (thalidomide) dosing should be
786 initiated at 100 to 300 mg/day, administered once daily with water, preferably at
787 bedtime and at least 1 hour after the evening meal. Patients weighing less than 50
788 kilograms should be started at the low end of the dose range.

789 In patients with a severe cutaneous ENL reaction, or in those who have previously
790 required higher doses to control the reaction, THALOMID[®] (thalidomide) dosing may
791 be initiated at higher doses up to 400 mg/day once daily at bedtime or in divided doses
792 with water, at least 1 hour after meals.

793 In patients with moderate to severe neuritis associated with a severe ENL reaction,
794 corticosteroids may be started concomitantly with THALOMID[®] (thalidomide). Steroid
795 usage can be tapered and discontinued when the neuritis has ameliorated.

796 Dosing with THALOMID[®] (thalidomide) should usually continue until signs and
797 symptoms of active reaction have subsided, usually a period of at least 2 weeks. Patients
798 may then be tapered off medication in 50 mg decrements every 2 to 4 weeks.

799 Patients who have a documented history of requiring prolonged maintenance treatment
800 to prevent the recurrence of cutaneous ENL or who flare during tapering, should be
801 maintained on the minimum dose necessary to control the reaction. Tapering off
802 medication should be attempted every 3 to 6 months, in decrements of 50 mg every 2 to
803 4 weeks.

804 HOW SUPPLIED

805 **(THIS PRODUCT IS ONLY SUPPLIED TO PHARMACISTS REGISTERED**
806 **WITH THE S.T.E.P.S.[®] PROGRAM - See BOXED WARNINGS.)**

807 THALOMID[®] (thalidomide) Capsules is supplied in the following dosages:

808 50 mg capsules [white opaque], imprinted “Celgene / 50 mg” with a “Do Not Get
809 Pregnant” logo.

810 Individual blister packs of 28 capsules (NDC 59572-205-14).

811 Boxes of 280 containing 10 prescription packs of 28 capsules each (NDC 59572-205-
812 94).

- 813 100 mg capsules [tan], imprinted “Celgene / 100 mg” with a “Do Not Get Pregnant”
814 logo.
815 Individual blister packs of 28 capsules (NDC 59572-210-15).
816 Boxes of 140 containing 5 prescription packs of 28 capsules each (NDC 59572-210-95).
817 200 mg capsules [blue], imprinted “Celgene / 200 mg” with a “Do Not Get Pregnant”
818 logo.
819 Individual blister packs of 28 capsules (NDC 59572-220-16).
820 Boxes of 84 containing 3 prescription packs of 28 capsules each (NDC 59572-220-96).

821 **STORAGE AND DISPENSING**

822 **PHARMACISTS NOTE:**

823 **BEFORE DISPENSING THALOMID[®] (thalidomide), YOU MUST ACTIVATE**
824 **THE AUTHORIZATION NUMBER ON EVERY PRESCRIPTION BY**
825 **CALLING THE CELGENE CUSTOMER CARE CENTER AT 1-888-4-**
826 **CELGENE (1-888-423-5436) AND OBTAINING A CONFIRMATION NUMBER.**
827 **YOU MUST ALSO WRITE THE CONFIRMATION NUMBER ON THE**
828 **PRESCRIPTION. YOU SHOULD ACCEPT A PRESCRIPTION ONLY IF IT**
829 **HAS BEEN ISSUED WITHIN THE PREVIOUS 7 DAYS (TELEPHONE**
830 **PRESCRIPTIONS ARE NOT PERMITTED); DISPENSE NO MORE THAN A 4-**
831 **WEEK (28-DAY) SUPPLY. A NEW PRESCRIPTION IS REQUIRED FOR**
832 **FURTHER DISPENSING. DISPENSE BLISTER PACKS INTACT (CAPSULES**
833 **CANNOT BE REPACKAGED); DISPENSE SUBSEQUENT PRESCRIPTIONS**
834 **ONLY IF FEWER THAN 7 DAYS OF THERAPY REMAIN ON THE**
835 **PREVIOUS PRESCRIPTION; AND EDUCATE ALL STAFF PHARMACISTS**
836 **ABOUT THE DISPENSING PROCEDURE FOR THALOMID[®] (thalidomide).**

837 This drug must not be repackaged.

838 Store at 25 ° C (77° F); excursions permitted to 15 – 30° C (59 -86° F). [See USP
839 Controlled Room Temperature]. Protect from light.

840 Rx only and only able to be prescribed and dispensed under the terms of the *S.T.E.P.S.*[®]
841 Restricted Distribution Program

842 Manufactured for Celgene Corporation

843 86 Morris Avenue

844 Summit, New Jersey 07901

845 1-(888) 423-5436

846 **Important Information and Warnings for All Patients Taking THALOMID[®]**
847 **(thalidomide)**

848 **WARNING: SEVERE, LIFE-THREATENING HUMAN BIRTH DEFECTS.**
849 **IF THALIDOMIDE IS TAKEN DURING PREGNANCY, IT CAN CAUSE**
850 **SEVERE BIRTH DEFECTS OR DEATH TO AN UNBORN BABY.**

851 **THALIDOMIDE SHOULD NEVER BE USED BY WOMEN WHO ARE**
 852 **PREGNANT OR WHO COULD BECOME PREGNANT WHILE TAKING THE**
 853 **DRUG. EVEN A SINGLE DOSE [1 CAPSULE (50 mg, 100 mg or 200 mg)]**
 854 **TAKEN BY A PREGNANT WOMAN CAN CAUSE SEVERE BIRTH DEFECTS**

855

856 **All Patients**

- 857 • The patient understands that severe birth defects can occur with the use of
 858 THALOMID[®] (thalidomide).
- 859 • The patient has been warned by his/her doctor that an unborn baby will almost
 860 certainly have severe birth defects and can even die, if a woman is pregnant or becomes
 861 pregnant while taking THALOMID[®] (thalidomide).
- 862 • THALOMID[®] (thalidomide) will be prescribed ONLY for the patient and must NOT
 863 be shared with ANYONE, even someone who has similar symptoms.
- 864 • THALOMID[®] (thalidomide) must be kept out of the reach of children and
 865 should NEVER be given to women who are able to have children.
- 866 • The patient cannot donate blood while taking THALOMID[®] (thalidomide).
- 867 • The patient has read the THALOMID[®] (thalidomide) patient brochure and/or
 868 viewed the videotape, “Important Information for Men and Women Taking
 869 THALOMID[®] (thalidomide)” and understands the contents, including other
 870 possible health problems from THALOMID[®] (thalidomide), “side effects.”
- 871 • The patient’s doctor has answered any questions the patient has asked.
- 872 • The patient must participate in a telephone survey and patient registry, while
 873 taking THALOMID[®] (thalidomide).

874

875 **Female Patients of Childbearing Potential**

- 876 • The patient must not take THALOMID[®] (thalidomide) if she is pregnant,
 877 breast-feeding a baby, or able to get pregnant and not using the required two
 878 methods of birth control.
- 879 • The patient confirms that she is not now pregnant, nor will she try to become
 880 pregnant during THALOMID[®] (thalidomide) therapy and for at least 4 weeks
 881 after she has completely finished taking THALOMID[®] (thalidomide).
- 882 • If the patient is able to become pregnant, she must use at least one highly
 883 effective method and one additional effective method of birth control
 884 (contraception) AT THE SAME TIME:

| | | | |
|-----|---|-------------------|--|
| 885 | At least one highly effective method | <u>AND</u> | One additional effective method |
| 886 | IUD | | Latex condom |
| 887 | Hormonal (birth control pills, injections, or implants) | | Diaphragm |
| 888 | Tubal ligation | | Cervical cap |
| 889 | Partner’s vasectomy | | |

- 890 • These birth control methods must be used for at least 4 weeks before beginning
891 THALOMID[®] (thalidomide) therapy, during THALOMID[®] (thalidomide) therapy,
892 and for 4 weeks following discontinuation of THALOMID[®] (thalidomide) therapy.
- 893 • The patient must use these birth control methods unless she completely abstains
894 from heterosexual sexual contact.
- 895 • If a hormonal method (birth control pills, injections, or implants) or IUD is not
896 medically possible for the patient, she may use another highly effective method or
897 two barrier methods AT THE SAME TIME.
- 898 • The patient must have a pregnancy test done by her doctor within the 24 hours prior
899 to starting THALOMID[®] (thalidomide) therapy, then every week during the first 4
900 weeks of THALOMID[®] (thalidomide) therapy.
- 901 • Thereafter, the patient must have a pregnancy test every 4 weeks if she has regular
902 menstrual cycles, or every 2 weeks if her cycles are irregular while she is taking
903 THALOMID[®] (thalidomide).
- 904 • The patient must immediately stop taking THALOMID[®] (thalidomide) and inform
905 her doctor:
 - 906 If she becomes pregnant while taking the drug
 - 907 If she misses her menstrual period, or experiences unusual menstrual bleeding
 - 908 If she stops using birth control
 - 909 If she thinks FOR ANY REASON that she may be pregnant
 - 910 The patient understands that if her doctor is not available, she can call 1-888-
911 668-2528 for information on emergency contraception

912 **Female Patients Not of Childbearing Potential**

- 913 • The patient certifies that she is not now pregnant, nor of childbearing potential as
914 she has been postmenopausal for at least 24 months (been through the change of
915 life); or she has had a hysterectomy.
- 916 • The patient or guardian certifies that a prepubertal female child is not now pregnant,
917 nor is of childbearing potential as menstruation has not yet begun, and/or the child
918 will not be engaging in heterosexual sexual contact for at least 4 weeks before
919 THALOMID[®] (thalidomide) therapy, during THALOMID[®] (thalidomide) therapy,
920 and for at least 4 weeks after stopping therapy.

921

922 **Male Patients**

- 923 • The patient has been told by his doctor that he must NEVER have unprotected
924 sexual contact with a woman who can become pregnant.
- 925 • Because THALOMID[®] (thalidomide) is present in semen, his doctor has explained
926 that he must either completely abstain from sexual contact with women who are
927 pregnant or able to become pregnant, or he must use a latex condom EVERY TIME

928 he engages in any sexual contact with women who are pregnant or may become
929 pregnant while he is taking THALOMID[®] (thalidomide) and for 4 weeks after he
930 stops taking the drug, even if he has had a successful vasectomy.

- 931 • The patient must inform his doctor:
932 If he has had unprotected sexual contact with a woman who can become
933 pregnant
934 If he thinks FOR ANY REASON, that his sexual partner may be pregnant.
935 The patient understands that if his doctor is not available, he can call 1-888-668-
936 2528 for information on emergency contraception
- 937 • The patient cannot donate semen or sperm while taking THALOMID[®]
938 (thalidomide).

939 **Authorization:**
940 This information has been read aloud to me in the language of my choice. I understand
941 that if I do not follow all of my doctor's instructions, I will not be able to receive
942 THALOMID[®] (thalidomide).
943 I now authorize my doctor to begin my treatment with THALOMID[®] (thalidomide).
944 Patient Signature _____ Date _____

945 I have fully explained to the patient the nature, purpose, and risks of the treatment
946 described above, especially the risks to women of childbearing potential. I have asked
947 the patient if he/she has any questions regarding his/her treatment with THALOMID[®]
948 (thalidomide) and have answered those questions to the best of my ability. I will comply
949 with all of my obligations and responsibilities as a prescriber registered under the
950 S.T.E.P.S.[®] restricted distribution program.

951 Prescriber Name (please type): _____
952 DEA Number: _____ Social Security Number if PA or NP: _____
953 Street Address: _____
954 City: _____ State: _____ Zip: _____
955 Prescriber Signature _____

956 **REFERENCES**

- 957 1. Manson JM. 1986. Teratogenicity. Cassarett and Doull's Toxicology: The Basic
958 Science of Poisons. Third Edition. Pages 195-220. New York: MacMillan
959 Publishing Co.
- 960 2. Smithels RW and Newman CG. 1992. J. Med. Genet. 29(10):716-723.
- 961 3. Sampaio EP, Kaplan G, Miranda A, *et al.* 1993. J. Infect. Dis. 168(2):408-414.
- 962 4. Sarno EN, Grau GE, Vieira LM, *et al.* 1991. Clin. Exp. Immunol. 84:103-108.
- 963 5. Sampaio EP, Moreira AL, Sarno EN, *et al.* 1992. J. Exp. Med. 175:1729-1737.

- 964 6. Nogueira AC, Neubert R, Helge H, *et al.* 1994. *Life Sciences*. 55(2):77-92.
- 965 7. Jacobson JM, Greenspan JS, Spritzler J, *et al.* 1997. *New Eng. J. Med.*
966 336(21):1487-1493
- 967 8. Eriksson T, Björkman S, Roth B, *et al.* 1998. *Chirality*. 10(3): 223-228.
- 968 9. Schumaker H, Smith RL, and Williams RT. 1965. *Br. J. Pharmacol.* 25:324-337.
- 969 10. Iyer CGS, Languillon J, Ramanujam K, *et al.* 1971. *Bull. WHO.* 45:719-732.
- 970 11. Sheskin J and Convit J. 1969. *Intl. J. Leprosy.* 37:135-146.
- 971 12. Waters MFR. 1971 *Lepr. Rev.* 42:26-42.
- 972 13. Unpublished data, on file at Celgene.
- 973
- 974 S.T.E.P.S.[®] is a registered trademark of Celgene Corporation.
- 975 U.S. Pat. Nos. 6,045,501 & 6,315,720.
- 976 THALPI. 010 XX/05 CG