

**1        WARNING: SEVERE, LIFE-THREATENING HUMAN BIRTH DEFECTS**

**2        IF THALIDOMIDE IS TAKEN DURING PREGNANCY, IT CAN CAUSE SEVERE**  
**3        BIRTH DEFECTS OR DEATH TO AN UNBORN BABY. THALIDOMIDE**  
**4        SHOULD NEVER BE USED BY WOMEN WHO ARE PREGNANT OR WHO**  
**5        COULD BECOME PREGNANT WHILE TAKING THE DRUG. EVEN A SINGLE**  
**6        DOSE [1 CAPSULE (50 mg)] TAKEN BY A PREGNANT WOMAN DURING HER**  
**7        PREGNANCY CAN CAUSE SEVERE BIRTH DEFECTS.**

**8        BECAUSE OF THIS TOXICITY AND IN AN EFFORT TO MAKE THE CHANCE**  
**9        OF FETAL EXPOSURE TO THALOMID AS NEGLIGIBLE AS POSSIBLE,**  
**10        THALOMID IS APPROVED FOR MARKETING ONLY UNDER A SPECIAL**  
**11        RESTRICTED DISTRIBUTION PROGRAM APPROVED BY THE FOOD AND**  
**12        DRUG ADMINISTRATION. THIS PROGRAM IS CALLED THE "SYSTEM FOR**  
**13        THALIDOMIDE EDUCATION AND PRESCRIBING SAFETY (S.T.E.P.S.)".**

**14        UNDER THIS RESTRICTED DISTRIBUTION PROGRAM, ONLY**  
**15        PRESCRIBERS AND PHARMACISTS REGISTERED WITH THE PROGRAM**  
**16        ARE ALLOWED TO PRESCRIBE AND DISPENSE THE PRODUCT. IN**  
**17        ADDITION, PATIENTS MUST BE ADVISED OF, AGREE TO, AND COMPLY**  
**18        WITH THE REQUIREMENTS OF THE S.T.E.P.S. PROGRAM IN ORDER TO**  
**19        RECEIVE PRODUCT.**

**20        PLEASE SEE THE FOLLOWING BOXED WARNINGS CONTAINING SPECIAL**  
**21        INFORMATION FOR PRESCRIBERS, FEMALE PATIENTS, AND MALE**  
**22        PATIENTS ABOUT THIS RESTRICTED DISTRIBUTION PROGRAM.**

**PRESCRIBERS**

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

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

Effective contraception (see **CONTRAINDICATIONS**) must be used for at least 1 month before beginning thalidomide therapy, during thalidomide therapy, and for 1 month following discontinuation of thalidomide therapy. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or because the patient has been post-menopausal for at least 24 months. Two reliable forms of contraception must be used simultaneously unless continuous abstinence from reproductive heterosexual sexual intercourse is the chosen method. Women of childbearing potential should be referred to a qualified provider of contraceptive methods, if needed. Sexually mature women who have not undergone a hysterectomy or who have not been post-menopausal for at least 24 consecutive months (i.e., who have had menses at some time in the preceding 24 consecutive months) are considered to be women of child-bearing potential.

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

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

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

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

15 July 1998

**FEMALE PATIENTS**

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

- she understands and can reliably carry out instructions.
- she is capable of complying with the mandatory contraceptive measures, pregnancy testing, patient registration, and patient survey as described in the System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*) program.
- she has received both oral and written warnings of the hazards of taking thalidomide during pregnancy and of exposing a fetus to the drug.
- she has received both oral and written warnings of the risk of possible contraception failure and of the need to use two reliable forms of contraception simultaneously (see **CONTRAINDICATIONS**), unless continuous abstinence from reproductive heterosexual intercourse is the chosen method. (Sexually mature women who have not undergone a hysterectomy or who have not been post-menopausal for at least 24 consecutive months (i.e., who have had menses at some time in the preceding 24 consecutive months) are considered to be women of child-bearing potential.).
- she acknowledges, in writing, her understanding of these warnings and of the need for using two reliable methods of contraception for one month prior to starting thalidomide therapy, during thalidomide therapy, and for one month after stopping thalidomide therapy.
- she has had a negative pregnancy test with a sensitivity of at least 50 mIU/mL, within the 24 hours prior to beginning therapy. (See **PRECAUTIONS, CONTRAINDICATIONS.**)
- if the patient is between 12 and 18 years of age, her parent or legal guardian must have read this material and agreed to ensure compliance with the above.

15 July 1998

89 **MALE PATIENTS**

90 Thalidomide is contraindicated in sexually mature MALES unless the PATIENT MEETS  
91 ALL OF THE FOLLOWING CONDITIONS:

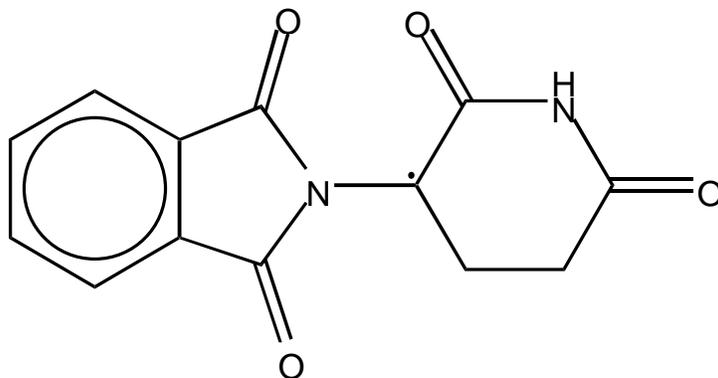
- 92 • he understands and can reliably carry out instructions.
- 93 • he is capable of complying with the mandatory contraceptive measures that are  
94 appropriate for men, patient registration, and patient survey as described in the  
95 *S.T.E.P.S.* program.
- 96 • he has received both oral and written warnings of the hazards of taking thalidomide and  
97 exposing a fetus to the drug.
- 98 • he has received both oral and written warnings of the risk of possible contraception  
99 failure and of the need to use barrier contraception when having sexual intercourse  
100 with women of childbearing potential, even if he has undergone successful vasectomy.
- 101 • he acknowledges, in writing, his understanding of these warnings and of the need for  
102 using barrier contraception (latex condom), even if he has undergone successful  
103 vasectomy, when having sexual intercourse with women of childbearing potential.  
104 Sexually mature women who have not undergone a hysterectomy or who have not  
105 been post-menopausal for at least 24 consecutive months (i.e., who have had menses at  
106 some time in the preceding 24 consecutive months) are considered to be women of  
107 child-bearing potential.
- 108 • if the patient is between 12 and 18 years of age, his parent or legal guardian must have  
109 read this material and agreed to ensure compliance with the above.

110 **DESCRIPTION**

111 THALOMID™ (thalidomide),  $\alpha$ -(N-phthalimido)glutarimide, is an immunomodulatory agent.  
112 The empirical formula for thalidomide is  $C_{13}H_{10}N_2O_4$  and the gram molecular weight is 258.2.  
113 The CAS number of thalidomide is 50-35-1.

114 **Chemical Structure of thalidomide**

15 July 1998



Note: • = asymmetric carbon atom

115  
116

117 Thalidomide is an off-white to white, nearly odorless, crystalline powder that is soluble at 25°C in  
 118 dimethyl sulfoxide and sparingly soluble in water and ethanol. The glutarimide moiety contains a  
 119 single asymmetric center and, therefore, may exist in either of two optically active forms  
 120 designated S-(-) or R-(+). THALOMID (thalidomide) is an equal mixture of the S-(-) and R-(+)  
 121 forms and, therefore, has a net optical rotation of zero.

122 THALOMID (thalidomide) is available in 50 mg capsules for oral administration. Active  
 123 ingredient: thalidomide. Inactive ingredients: anhydrous lactose, microcrystalline cellulose,  
 124 polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

## 125 CLINICAL PHARMACOLOGY

### 126 Mechanism of Action

127 Thalidomide is an immunomodulatory agent with a spectrum of activity that is not fully  
 128 characterized. In patients with erythema nodosum leprosum (ENL) the mechanism of action is  
 129 not fully understood.

130 Available data from *in vitro* studies and preliminary clinical trials suggest that the immunologic  
 131 effects of this compound can vary substantially under different conditions, but, may be related to  
 132 suppression of excessive tumor necrosis factor-alpha (TNF- $\alpha$ ) production and down-modulation  
 133 of selected cell surface adhesion molecules involved in leukocyte migration<sup>3,4,5,6</sup>. For example,  
 134 administration of thalidomide has been reported to decrease circulating levels of TNF- $\alpha$  in  
 135 patients with ENL<sup>3</sup>, however, it has also been shown to increase plasma TNF- $\alpha$  levels in HIV-  
 136 seropositive patients<sup>7</sup>.

### 137 Pharmacokinetics and Drug Metabolism

#### 138 Absorption

139 The absolute bioavailability of thalidomide from THALOMID capsules has not yet been  
 140 characterized in human subjects due to its poor aqueous solubility. In studies of both healthy  
 141 volunteers and subjects with Hansen's disease, the mean time to peak plasma concentrations  
 142 ( $T_{max}$ ) of THALOMID ranged from 2.9 to 5.7 hours indicating that THALOMID is slowly  
 143 absorbed from the gastrointestinal tract. While the extent of absorption (as measured by area

15 July 1998

144 under the curve [AUC]) is proportional to dose in healthy subjects, the observed peak  
145 concentration ( $C_{max}$ ) increased in a less than proportional manner (see Table 1 below). This lack  
146 of  $C_{max}$  dose proportionality, coupled with the observed increase in  $T_{max}$  values, suggests that the  
147 poor solubility of thalidomide in aqueous media may be hindering the rate of absorption.

148 **Table 1**  
149 **Pharmacokinetic Parameter Values for THALOMID (thalidomide)**  
150 **Mean (%CV)**

| Population/<br>Single Dose           | AUC <sub>0</sub><br>( $\mu\text{g hr/mL}$ ) | $C_{max}$<br>( $\mu\text{g/mL}$ ) | $T_{max}$<br>(hrs) | Half-life<br>(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%)         |

159 Co-administration of THALOMID with a high fat meal causes minor (<10%) changes in the  
160 observed AUC and  $C_{max}$  values: however, it causes an increase in  $T_{max}$  to approximately 6 hours.

161 ***Distribution***

162 **It is not known whether thalidomide is present in the ejaculate of males.**

163 The extent of plasma protein binding of thalidomide is unknown.

164 ***Metabolism***

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

171 ***Elimination***

172 As indicated in Table 1 (above) the mean half-life of elimination ranges from approximately 5 to 7  
173 hours following a single dose and is not altered upon multiple dosing. As noted in the metabolism  
174 subsection, the precise metabolic fate and route of elimination of thalidomide in humans is not known  
175 at this time. Thalidomide itself has a renal clearance of 1.15 mL/minute with less than 0.7% of the  
176 dose excreted in the urine as unchanged drug. Following a single dose, urinary levels of thalidomide  
177 were undetectable 48 hrs after dosing. Although thalidomide is thought to be hydrolyzed to a number  
178 of metabolites<sup>8</sup>, only a very small amount (0.02% of the administered dose) of 4-OH-thalidomide was  
179 identified in the urine of subjects 12 to 24 hours after dosing.

180 ***Pharmacokinetic Data in Special Populations***

181 ***HIV-seropositive Subjects:*** There is no apparent significant difference in measured pharmacokinetic

15 July 1998

182 parameter values between healthy human subjects and HIV-seropositive subjects following single  
183 dose administration of THALOMID (thalidomide) capsules.

184 *Patients with Hansen's Disease:* Analysis of data from a small study in Hansen's patients suggests  
185 that these patients, relative to healthy subjects, may have an increased bioavailability of THALOMID.  
186 The increase is reflected both in an increased area under the curve and in increased peak plasma  
187 levels. The clinical significance of this increase is unknown.

188 *Patients with Renal Insufficiency:* The pharmacokinetics of thalidomide in patients with renal  
189 dysfunction have not been determined.

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

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

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

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

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

199 ***Clinical Studies***

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

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

206 **Table 2**  
207 **Double Blind, Controlled Clinical Trials of Thalidomide in Patients with ENL:**  
208 **Cutaneous Response**

209

| Reference  | No. of Patients | No. Treatment Courses* | Percent Responding** |                |
|--|-----------------|------------------------|----------------------|----------------|
| Iyer <i>et al.</i> <sup>9</sup><br>Bull World Health<br>Organization 1971;<br>45:719 | 92              | 204                    | Thalidomide<br>75%   | Aspirin<br>25% |
| Sheskin <i>et al.</i> <sup>10</sup><br>Int J Lep 1969; 37:135                        | 52              | 173                    | Thalidomide<br>66%   | Placebo<br>10% |

210 \* In patients with cutaneous lesions

211 \*\* Iyer: Complete response or lesions absent

212



15 July 1998

252 must commit either to abstain continuously from heterosexual sexual intercourse or to use two  
 253 methods of reliable birth control, including at least one highly effective method (*e.g.*, IUD,  
 254 hormonal contraception, tubal ligation, or partner's vasectomy) and one additional effective  
 255 method (*e.g.*, latex condom, diaphragm, or cervical cap), beginning 4 weeks prior to initiating  
 256 treatment with thalidomide, during therapy with thalidomide, and continuing for 4 weeks  
 257 following discontinuation of thalidomide therapy. If hormonal or IUD contraception is medically  
 258 contraindicated (see also **PRECAUTIONS: DRUG INTERACTIONS**), two other effective or  
 259 highly effective methods may be used.

260 Women of childbearing potential being treated with thalidomide should have pregnancy testing  
 261 (sensitivity of at least 50 mIU/mL). The test should be performed within the 24 hours before  
 262 beginning thalidomide therapy and then weekly during the first month of thalidomide therapy, then  
 263 monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with  
 264 irregular menstrual cycles. Pregnancy testing and counseling should be performed if a patient  
 265 misses her period or if there is any abnormality in menstrual bleeding. If pregnancy occurs during  
 266 thalidomide treatment, thalidomide must be immediately discontinued. Under these conditions,  
 267 the patient should be referred to an obstetrician / gynecologist experienced in reproductive  
 268 toxicity for further evaluation and counseling.

269 THALOMID (thalidomide) is contraindicated in patients who have demonstrated hypersensitivity  
 270 to the drug and its components.

271 **WARNINGS (See BOXED WARNINGS.)**

272 **Birth defects:**

273 Thalidomide can cause severe birth defects in humans. (See **BOXED WARNING** and  
 274 **CONTRAINDICATIONS**.) Patients should be instructed to take thalidomide only as prescribed  
 275 and not to share their thalidomide with anyone else. Because it is not known whether or not  
 276 thalidomide is present in the ejaculate of males receiving the drug, males receiving thalidomide  
 277 must always use a latex condom when engaging in sexual activity with women of childbearing  
 278 potential.

279 **Drowsiness and somnolence:**

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

285 **Peripheral neuropathy:**

286 Thalidomide is known to cause nerve damage that may be permanent. Peripheral neuropathy is a  
 287 common, potentially severe, side effect of treatment with thalidomide that may be irreversible.  
 288 Peripheral neuropathy generally occurs following chronic use over a period of months, however,  
 289 reports following relatively short term use also exist. The correlation with cumulative dose is

15 July 1998

290 unclear. Symptoms may occur some time after thalidomide treatment has been stopped and may  
 291 resolve slowly or not at all. Few reports of neuropathy have arisen in the treatment of ENL  
 292 despite long-term thalidomide treatment. However, the inability clinically to differentiate  
 293 thalidomide neuropathy from the neuropathy often seen in Hansen's disease makes it difficult to  
 294 determine accurately the incidence of thalidomide-related neuropathy in ENL patients treated with  
 295 thalidomide.

296 Patients should be examined at monthly intervals for the first 3 months of thalidomide therapy to  
 297 enable the clinician to detect early signs of neuropathy, which include numbness, tingling or pain  
 298 in the hands and feet. Patients should be evaluated periodically thereafter during treatment.  
 299 Patients should be regularly counseled, questioned, and evaluated for signs or symptoms of  
 300 peripheral neuropathy. Consideration should be given to electrophysiological testing, consisting  
 301 of measurement of sensory nerve action potential (SNAP) amplitudes at baseline and thereafter  
 302 every 6 months in an effort to detect asymptomatic neuropathy. If symptoms of drug-induced  
 303 neuropathy develop, thalidomide should be discontinued immediately to limit further damage, if  
 304 clinically appropriate. Usually, treatment with thalidomide should only be reinitiated if the  
 305 neuropathy returns to baseline status. Medications known to be associated with neuropathy  
 306 should be used with caution in patients receiving thalidomide.

307 **Dizziness and orthostatic hypotension:**

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

311 **Neutropenia:**

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

319 **Increased HIV-Viral Load:**

320 In a randomized, placebo controlled trial of thalidomide in an HIV-seropositive patient  
 321 population, plasma HIV RNA levels were found to increase (median change =  $0.42 \log_{10}$  copies  
 322 HIV RNA/mL,  $p = 0.04$  compared to placebo)<sup>7</sup>. A similar trend was observed in a second,  
 323 unpublished study conducted in patients who were HIV-seropositive<sup>12</sup>. The clinical significance of  
 324 this increase is unknown. Both studies were conducted prior to availability of highly active  
 325 antiretroviral therapy. Until the clinical significance of this finding is further understood, in HIV-  
 326 seropositive patients, viral load should be measured after the first and third months of treatment  
 327 and every 3 months thereafter.

15 July 1998

328 **PRECAUTIONS**

329 **Hypersensitivity:**

330 Hypersensitivity to THALOMID (thalidomide) has been reported. Signs and symptoms have  
331 included the occurrence of erythematous macular rash, possibly associated with fever,  
332 tachycardia, and hypotension, and if severe, may necessitate interruption of therapy. If the  
333 reaction recurs when dosing is resumed, THALOMID (thalidomide) should be discontinued.

334 **Bradycardia:**

335 Bradycardia in association with thalidomide use has been reported. At present there have been  
336 no reports of bradycardia requiring medical or other intervention. The clinical significance and  
337 underlying etiology of the bradycardia noted in some thalidomide-treated patients are present  
338 unknown.

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

340 Patient should be instructed about the potential teratogenicity of thalidomide and the precautions  
341 that must be taken to preclude fetal exposure as per the S.T.E.P.S. program and boxed warnings  
342 in this package insert. Patients should be instructed to take thalidomide only as prescribed in  
343 compliance with all of the provisions of the S.T.E.P.S. Restricted Distribution Program.

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

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

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

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

357 Patients should be instructed that they are not permitted to donate blood while taking thalidomide.  
358 In addition, male patients should be instructed that they are not permitted to donate sperm while  
359 taking thalidomide.

360 **Laboratory Tests**

361 ***Pregnancy Testing:*** (See BOXED WARNINGS.) Women of childbearing potential should have

15 July 1998

362 pregnancy testing performed (sensitivity of at least 50 mIU/mL). The test should be performed  
363 within the 24 hours prior to beginning thalidomide therapy and then weekly during the first month  
364 of use, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in  
365 women with irregular menstrual cycles. Pregnancy testing should also be performed if a patient  
366 misses her period or if there is any abnormality in menstrual bleeding.

367 *Neutropenia:* (See WARNINGS.)

368 *HIV Viral Load:* (See WARNINGS.)

### 369 **Drug Interactions**

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

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

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

### 378 **Important Non-Thalidomide Drug Interactions**

379 *Drugs That Interfere with Hormonal Contraceptives:* Concomitant use of HIV-protease  
380 inhibitors, griseofulvin, rifampin, rifabutin, phenytoin, or carbamazepine with hormonal  
381 contraceptive agents, may reduce the effectiveness of the contraception. Therefore, women  
382 requiring treatment with one or more of these drugs must use two OTHER effective or highly  
383 effective methods of contraception or abstain from reproductive heterosexual sexual intercourse.

### 384 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

385 Long-term carcinogenicity tests have not been conducted using thalidomide. Thalidomide gave  
386 no evidence of mutagenic effects when assayed in *in vitro* bacterial (*Salmonella typhimurium* and  
387 *Escherichia coli*; Ames mutagenicity test), *in vitro* mammalian (AS52 Chinese hamster ovary  
388 cells; AS52/XPRT mammalian cell forward gene mutation assay) and *in vivo* mammalian (CD-1  
389 mice; *in vivo* micronucleus test) test systems.

390 Animal studies to characterize the effects of thalidomide on fertility have not been conducted.

### 391 **Pregnancy**

392 *Pregnancy Category X:* See **BOXED WARNING** and **CONTRAINDICATIONS**.

393 Because of the known human teratogenicity of thalidomide, thalidomide is contraindicated in  
394 women who are or may become pregnant and who are not using the two required types of birth

15 July 1998

395 control or who are not continually abstaining from reproductive heterosexual sexual intercourse.  
 396 If thalidomide is taken during pregnancy, it can cause severe birth defects or death to an unborn  
 397 baby. Thalidomide should never be used by women who are pregnant or who could become  
 398 pregnant while taking the drug. Even a single dose [1 capsule (50 mg)] taken by a pregnant  
 399 woman can cause birth defects. If pregnancy does occur during treatment, the drug should be  
 400 immediately discontinued. Under these conditions, the patient should be referred to an  
 401 obstetrician / gynecologist experienced in reproductive toxicity for further evaluation and  
 402 counselling. Any suspected fetal exposure to THALOMID (thalidomide) must be reported to the  
 403 FDA *via* the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation.

404 Animal studies to characterize the effects of thalidomide on late stage pregnancy have not been  
 405 conducted.

406 **Use in Nursing Mothers**

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

411 **Pediatric Use**

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

413 **Geriatric Use**

414 No systematic studies in geriatric patients have been conducted. Thalidomide has been used in  
 415 clinical trials in patients up to 90 years of age. Adverse events in patients over the age of 65 years  
 416 did not appear to differ in kind from those reported for younger individuals.

417 **ADVERSE REACTIONS**

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

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

427 Hypersensitivity to THALOMID (thalidomide) and bradycardia in patients treated with  
 428 thalidomide have been reported. (See **PRECAUTIONS**.)

429 Somnolence, dizziness, and rash are the most commonly observed adverse events associated with  
 430 the use of thalidomide. Thalidomide has been studied in controlled and uncontrolled clinical trials

15 July 1998

---

431 in patients with ENL and in people who are HIV-seropositive. In addition, thalidomide has been  
432 administered investigationally for more than 20 years in numerous indications. Adverse event  
433 profiles from these uses are summarized in the sections that follow.

434 **Other Adverse Events:**

435 Due to the nature of the longitudinal data that form the basis of this product's safety evaluation,  
436 no determination has been made of the causal relationship between the reported adverse events  
437 listed below and thalidomide. These lists are of various adverse events noted by investigators in  
438 patients to whom they had administered thalidomide under various conditions.

439 **Incidence in Controlled Clinical Trials**

440 Table 4 lists treatment-emergent signs and symptoms that occurred in THALOMID-treated  
441 patients in controlled clinical trials in ENL. Doses ranged from 50 to 300 mg/day. All adverse  
442 events were mild to moderate in severity, and none resulted in discontinuation. Table 4 also lists  
443 treatment-emergent adverse events that occurred in at least 3 of the THALOMID-treated  
444 HIV-seropositive patients who participated in an 8-week, placebo controlled clinical trial. Events  
445 that were more frequent in the placebo-treated group are not included. (See **WARNINGS,**  
446 **PRECAUTIONS,** and **DRUG INTERACTIONS.**)

15 July 1998

**Table 4**  
**Summary of Adverse Events (AEs)**  
**Reported in Celgene-sponsored Controlled Clinical Trials**

| Body System/Adverse Event                   | All AEs Reported<br>in ENL Patients | AEs Reported in HIV-seropositive Patients |                      |                   |
|---|-------------------------------------|---|----------------------|-------------------|
|   |                                     | Thalidomide                               |                      | Placebo<br>(N=35) |
|   |                                     | 50 to 300 mg/day<br>(N=24)                | 100 mg/day<br>(N=36) |                   |
| <b>Body as a Whole</b>                      | <b>16 (66.7%)</b>                   | <b>18 (50.0%)</b>                         | <b>19 (59.4%)</b>    | <b>13 (37.1%)</b> |
| 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%)          |
| <b>Digestive System</b>                     | <b>5 (20.8%)</b>                    | <b>16 (44.4%)</b>                         | <b>16 (50.0%)</b>    | <b>15 (42.9%)</b> |
| 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                 |
| <b>Hemic and Lymphatic</b>                  | <b>0</b>                            | <b>8 (22.2%)</b>                          | <b>13 (40.6%)</b>    | <b>10 (28.6%)</b> |
| Anemia                                      | 0                                   | 2 (5.6%)                                  | 4 (12.5%)            | 3 (8.6%)          |
| Leukopenia                                  | 0                                   | 6 (16.7%)                                 | 8 (25.0%)            | 3 (8.6%)          |
| Lymphadenopathy                             | 0                                   | 2 (5.6%)                                  | 4 (12.5%)            | 3 (8.6%)          |
| <b>Metabolic and Endocrine Disorders</b>    | <b>1 (4.2%)</b>                     | <b>8 (22.2%)</b>                          | <b>12 (37.5%)</b>    | <b>8 (22.9%)</b>  |
| 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%)          |
| <b>Nervous System</b>                       | <b>13 (54.2%)</b>                   | <b>19 (52.8%)</b>                         | <b>18 (56.3%)</b>    | <b>12 (34.3%)</b> |
| 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                 |
| <b>Respiratory System</b>                   | <b>3 (12.5%)</b>                    | <b>9 (25.0%)</b>                          | <b>6 (18.7%)</b>     | <b>9 (25.7%)</b>  |
| 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%)          |
| <b>Skin and Appendages</b>                  | <b>10 (41.7%)</b>                   | <b>17 (47.2%)</b>                         | <b>18 (56.3%)</b>    | <b>19 (54.3%)</b> |
| 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%)         |
| <b>Urogenital System</b>                    | <b>2 (8.3%)</b>                     | <b>6 (16.7%)</b>                          | <b>2 (6.3%)</b>      | <b>4 (11.4%)</b>  |
| 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                 |

15 July 1998

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

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

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

522 ***Cardiovascular System:*** Bradycardia, hypertension, hypotension, peripheral vascular disorder,  
523 tachycardia.

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

526 ***Hemic and Lymphatic:*** ESR decrease, eosinophilia, granulocytopenia, hypochromic anemia,  
527 leukemia, leukocytosis, leukopenia, MCV elevated, RBC abnormal, spleen palpable,  
528 thrombocytopenia.

529 ***Metabolic and Endocrine:*** ADH inappropriate, alkaline phosphatase, amyloidosis, bilirubinemia,  
530 BUN increased, creatinine increased, cyanosis, diabetes, edema, electrolyte abnormalities,  
531 hyperglycemia, hyperkalemia, hyperuricemia, hypocalcemia, hypoproteinemia, LDH increased,  
532 phosphorus decreased, SGPT increased.

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

535 ***Nervous System:*** Abnormal thinking, agitation, amnesia, anxiety, causalgia, circumoral  
536 paresthesia, confusion, depression, euphoria, hyperesthesia, insomnia, nervousness, neuralgia,  
537 neuritis, neuropathy, paresthesia, peripheral neuritis, psychosis, vasodilation.

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

540 ***Skin and Appendages:*** Acne, alopecia, dry skin, eczematous rash, exfoliative dermatitis,  
541 ichthyosis, perifollicular thickening, skin necrosis, seborrhea, sweating, urticaria, vesiculobullous  
542 rash.

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

544 ***Urogenital:*** Decreased creatinine clearance, hematuria, orchitis, proteinuria, pyuria, urinary

15 July 1998

545 frequency.

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

547 In addition to controlled clinical trials, THALOMID has been used in uncontrolled studies in 145  
548 patients. Less frequent adverse events that have been reported in these HIV-seropositive patients  
549 treated with THALOMID were grouped into a smaller number of standardized categories using  
550 modified COSTART dictionary / terminology and these categories are used in the listing below.  
551 Adverse events that have already been included in the tables and narrative above, that are too  
552 general to be informative.

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

556 **Cardiovascular System:** Angina pectoris, arrhythmia, atrial fibrillation, bradycardia, cerebral  
557 ischemia, cerebrovascular accident, congestive heart failure, deep thrombophlebitis, heart arrest,  
558 heart failure, hypertension, hypotension, murmur, myocardial infarct, palpitation, pericarditis,  
559 peripheral vascular disorder, postural hypotension, syncope, tachycardia, thrombophlebitis,  
560 thrombosis.

561 **Digestive System:** Cholangitis, cholestatic jaundice, colitis, dyspepsia, dysphagia, esophagitis,  
562 gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, gum disorder, hepatitis,  
563 pancreatitis, parotid gland enlargement, periodontitis, stomatitis, tongue discoloration, tooth  
564 disorder.

565 **Hemic and Lymphatic:** Aplastic anemia, macrocytic anemia, megaloblastic anemia, microcytic  
566 anemia.

567 **Metabolic and Endocrine:** Avitaminosis, bilirubinemia, dehydration, hypercholesteremia,  
568 hyperlipemia, increased alkaline phosphatase, increased lipase, increased serum creatinine,  
569 peripheral edema.

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

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

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

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

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

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

15 July 1998

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

#### 587 **DRUG ABUSE AND DEPENDENCE**

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

#### 591 **OVERDOSAGE**

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

#### 595 **DOSAGE AND ADMINISTRATION**

596 **THALOMID MUST ONLY BE ADMINISTERED IN COMPLIANCE WITH ALL OF**  
597 **THE TERMS OUTLINED IN THE S.T.E.P.S. PROGRAM. THALOMID MAY ONLY**  
598 **BE PRESCRIBED BY PRESCRIBERS REGISTERED WITH THE S.T.E.P.S.**  
599 **PROGRAM AND MAY ONLY BE DISPENSED BY PHARMACISTS REGISTERED**  
600 **WITH THE S.T.E.P.S. PROGRAM.**

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

603 For an episode of cutaneous ENL, THALOMID dosing should be initiated at 100 to 300 mg/day,  
604 administered once daily with water, preferably at bedtime and at least 1 hour after the evening  
605 meal. Patients weighing less than 50 kilograms should be started at the low end of the dose  
606 range.

607 In patients with a severe cutaneous ENL reaction, or in those who have previously required  
608 higher doses to control the reaction, THALOMID dosing may be initiated at higher doses up to  
609 400 mg/day once daily at bedtime or in divided doses with water, at least 1 hour after meals.

610 In patients with moderate to severe neuritis associated with a severe ENL reaction,  
611 corticosteroids may be started concomitantly with THALOMID. Steroid usage can be tapered  
612 and discontinued when the neuritis has ameliorated.

613 Dosing with THALOMID should usually continue until signs and symptoms of active reaction

15 July 1998

614 have subsided, usually a period of at least 2 weeks. Patients may then be tapered off medication  
615 in 50 mg decrements every 2 to 4 weeks.

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

## 620 HOW SUPPLIED

621 **(THIS PRODUCT IS ONLY SUPPLIED TO PHARMACISTS REGISTERED WITH THE**  
622 **S.T.E.P.S. PROGRAM - See BOXED WARNINGS.)**

623 THALOMID (thalidomide) is supplied in hard gelatin, 50 mg capsules [white opaque], imprinted  
624 “Celgene” with a “do not get pregnant” logo. Boxes containing six prescription packs of 14  
625 capsules each (84 capsules total).

626 NDC Number(s)  
627 59572-105-02

## 628 STORAGE AND DISPENSING

### 629 PHARMACISTS NOTE:

630 **DRUG MUST ONLY BE DISPENSED IN NO MORE THAN A 1-MONTH SUPPLY**  
631 **AND ONLY ON PRESENTATION OF A NEW PRESCRIPTION WRITTEN WITHIN**  
632 **THE PREVIOUS 14 DAYS. SPECIFIC INFORMED CONSENT (copy attached as part**  
633 **of this package insert) AND COMPLIANCE WITH THE MANDATORY PATIENT**  
634 **REGISTRY AND SURVEY ARE REQUIRED FOR ALL PATIENTS (MALE AND**  
635 **FEMALE) PRIOR TO DISPENSING BY THE PHARMACIST.**

636 This drug must not be repackaged.

637 Store at 59 to 86°F; 15 to 30°C. Protect from light.

638 Rx only and only able to be prescribed and dispensed under the terms of the S.T.E.P.S. Restricted  
639 Distribution Program

640 Manufactured by Celgene Corporation  
641 7 Powder Horn Drive  
642 Warren, New Jersey 07059

643 **Important Information and Warnings For All Patients Taking THALOMID™**  
644 **(thalidomide)**

645

**WARNING: SERIOUS HUMAN BIRTH DEFECTS**

646

**IF THALIDOMIDE IS TAKEN DURING PREGNANCY, IT CAN CAUSE SEVERE BIRTH DEFECTS OR DEATH TO AN UNBORN BABY. THALIDOMIDE SHOULD NEVER BE USED BY WOMEN WHO ARE PREGNANT OR WHO COULD BECOME PREGNANT WHILE TAKING THE DRUG. EVEN A SINGLE DOSE [1 CAPSULE (50 mg)] TAKEN BY A PREGNANT WOMAN CAN CAUSE SEVERE BIRTH DEFECTS.**

647

648

649

650

651

652

**CONSENT FOR WOMEN:**

653

INIT: \_\_\_ 1. I understand that I must not take THALOMID™ (thalidomide) if I am pregnant, breast-feeding a baby, or able to get pregnant and not using the required two methods of birth control.

654

655

INIT: \_\_\_ 2. I understand that severe birth defects can occur with the use of THALOMID™ (thalidomide). I have been warned by my doctor that my unborn baby will almost certainly have serious birth defects or may even die if I am pregnant or become pregnant while taking THALOMID™ (thalidomide).

656

657

658

INIT: \_\_\_ 3. I understand that if I am able to become pregnant, I must use at least one highly effective method and one additional effective method of birth control (contraception) **AT THE SAME TIME:**

659

**At least one highly effective method**

**One additional effective method**

660

IUD

**AND**

Latex condom

661

Hormonal (Birth control pills)

Diaphragm

662

Tubal ligation

Cervical cap

663

Partner's vasectomy

664

These birth control methods must be used for at least 4 weeks before starting THALOMID therapy, all during THALOMID therapy, and for at least 4 weeks after THALOMID therapy has stopped. I must use these methods even if I am infertile, unless I have had a hysterectomy or because I have been post-menopausal for at least 24 months (been through the changes of life). The only exception is if I completely avoid heterosexual sexual intercourse. If a hormonal (birth control pills) or IUD method is not medically possible for me, I may use another highly effective method or two barrier methods **AT THE SAME TIME**.

665

666

667

668

669

670

671

INIT: \_\_\_ 4. I know that I must have a pregnancy test done by my doctor within the 24 hours prior to starting THALOMID therapy, then every week during the first 4 weeks of THALOMID therapy. I will then have a pregnancy test every 4 weeks if I have regular menstrual cycles, or every 2 weeks if my cycles are irregular while I am taking THALOMID.

672

INIT: \_\_\_ 5. I know that I must immediately stop taking THALOMID™ and inform my doctor if I become pregnant while taking the drug; if I miss my menstrual period, or experience unusual menstrual bleeding; stop using birth control; or think, **FOR ANY REASON**, that I may be pregnant. If my doctor is not available, I can call 1-888-668-2528 for information on emergency contraception.

673

674

675

INIT: \_\_\_ 6. I am not now pregnant, nor will I try to become pregnant for at least 4 weeks after I have completely finished taking THALOMID™.

676

INIT: \_\_\_ 7. I understand that THALOMID™ will be prescribed **ONLY** for me. I must **NOT** share it with **ANYONE**, even someone who has symptoms similar to mine. It must be kept out of the reach of children and should never be given to women who are able to have children.

677

678

679

INIT: \_\_\_ 8. I have read the THALOMID™ patient brochure and/or viewed the videotape, "Important Information for Men and Women Taking THALOMID™ (thalidomide)". I understand the contents, including other possible health problems from THALOMID™, so-called "side effects". I know that I cannot donate blood while taking THALOMID™.

680

681

INIT: \_\_\_ 9. My doctor has answered any questions I have asked.

682

INIT: \_\_\_ 10. I understand that I must participate in a survey and patient registry while I am on THALOMID™, which will require completing additional forms.

683

684

685

686

687

688

689

692  
693  
694  
695  
696  
697  
698  
699  
700  
701  
702  
703  
704  
705  
706  
707  
708  
709  
710  
711  
712  
713  
714

**CONSENT FOR MEN:**

INIT:\_\_\_ 1. I understand that I must not take THALOMID™ if I cannot avoid unprotected sex with a woman , even if I have had a successful vasectomy.

INIT:\_\_\_ 2. I understand that severe birth defects or death to an unborn baby have occurred when women took thalidomide during pregnancy.

INIT:\_\_\_ 3. I have been told by my doctor that I must NEVER have unprotected sex with a woman because it is not known if the drug is present in semen or sperm. My doctor has explained that I must either completely avoid heterosexual sexual intercourse or I must use a latex condom EVERY TIME I have sexual intercourse with a female partner while I am taking THALOMID™ - and for 4 weeks after I stop taking the drug, even if I have had a successful vasectomy.

INIT:\_\_\_ 4. I also know that I must inform my doctor if I have had unprotected sex with a woman; or if I think, FOR ANY REASON, that my sexual partner may be pregnant. If my doctor is not available, I can call 1-888-668-2528 for information on emergency contraception.

INIT:\_\_\_ 5. I understand that THALOMID™ will be prescribed ONLY for me. I must NOT share it with ANYONE, even someone who has symptoms similar to mine. It must be kept out of the reach of children and should never be given to women who are able to have children.

INIT:\_\_\_ 6. I have read the THALOMID™ patient brochure and/or viewed the videotape, “Important Information for Men and Women Taking THALOMID™ (thalidomide)”. I understand the contents, including other possible health problems from THALOMID™ (thalidomide), so-called “side effects”. I know that I cannot donate blood or semen while taking THALOMID™ (thalidomide).

INIT:\_\_\_ 7. My doctor has answered any questions I have asked.

INIT:\_\_\_ 8. I understand that I must participate in a survey and patient registry while I am on THALOMID™, which will require completing additional forms.

715  
716  
717  
718  
719  
720  
721  
722  
723  
724  
725  
726  
727  
728  
729  
730  
731  
732

**Authorization:**

This information has been read aloud to me in the language of my choice. I understand that if I do not follow all of my doctor’s instructions, I will not be able to receive THALOMID™ . I now authorize my doctor to begin my treatment with THALOMID™ .

---

|                             |  |                                |
|-----------------------------|--|--------------------------------|
| Patient Name (please print) | Social Security No.<br>(Only last six digits required) | Date of Birth<br>(mo./day/yr.) |
|-----------------------------|--|--------------------------------|

---

Patient, Parent / Guardian Signature \_\_\_\_\_ Date (mo./day/yr.) \_\_\_\_\_

I have fully explained to the patient the nature, purpose, and risks of the treatment described above, especially the risks to women of childbearing potential. I have asked the patient if she/he has any questions regarding her/his treatment with THALOMID™ and have answered those questions to the best of my ability. I will ensure that the appropriate components of the patient consent form are completed. In addition, I will comply with all of my obligations and responsibilities as a prescriber registered under the S.T.E.P.S. restricted distribution program.

---

|                               |         |
|-------------------------------|---------|
| Physician Name (please print) | DEA No. |
|-------------------------------|---------|

---

Physician Signature \_\_\_\_\_ Date (mo./day/yr.) \_\_\_\_\_

733  
734  
735

**REFERENCES**

1. Manson JM. 1986. Teratogenicity. Cassarett and Doull’s Toxicology: The Basic Science of Poisons. Third Edition. Pages 195-220. New York: MacMillan Publishing Co.

15 July 1998

- 
- 736 2. Smithels RW and Newman CG. 1992. *J. Med. Genet.* 29(10):716-723.
- 737 3. Sampaio EP, Sarno EN, Galilly R, *et al.* 1992. *J. Exp. Med.* 168:408-414.
- 738 4. Sarno EN, Grau GE, Vieira LM, *et al.* 1991. *Clin. Exp. Immunol.* 84:103-108.
- 739 5. Sampaio EP, Moreira AL, Sarno EN, *et al.* 1992. *J. Exp. Med.* 175:1729-1737.
- 740 6. Nogueira AC, Neubert R, Helge H, *et al.* 1994. *Life Sciences.* 55(2):77-92.
- 741 7. Jacobson JM, Greenspan JS, Spritzler J, *et al.* 1997. *New Eng. J. Med.* 336(21):1487-  
 742 1493.
- 743 8. Schumaker H, Smith RL, and Williams RT. 1965. *Br. J. Pharmacol.* 25:324-337.
- 744 9. Iyer CGS, Languillon J, Ramanujam K, *et al.* 1971. *Bull. WHO.* 45:719-732.
- 745 10. Sheskin J and Convit J. 1969. *Intl. J. Leprosy.* 37:135-146.
- 746 11. Waters MFR. 1971. *Lepr. Rev.* 42:26-42.
- 747 12. Unpublished data, on file at Celgene.