

Reviewer's Comment: Grade 3/4 thalidomide toxicities did not appear to have a predilection for either gender.

The gender distribution of the 25 patients in the Thal/Dex treatment arm and 18 patients in the dexamethasone-alone arm whom I adjudicated as having met the primary endpoint of ECOG CR, NCR, or PR at 4 months are presented below in Reviewer's Table 53.

Reviewer's Table 53: Gender of Study E1A00 patients by efficacy (ITT pop.)

Gender	Thal/Dex (n = 103)		Dex alone (n = 104)	
	Responders	Nonresponders	Responders	Nonresponders
Female	10 (10 %)	38 (37 %)	10 (10 %)	32 (31 %)
Male	15 (15 %)	40 (39 %)	8 (8 %)	53 (51 %)
Unknown	0	0	0	1

Reviewer's Comment: Male gender appeared to correlate with responsiveness to Thal/Dex. Because Study E1A00 was not designed to assess the relationship between response and gender, this observation can only serve as hypothesis generating.

Reviewer's Table 54: Treatment-related grade 3/4 toxicity by baseline creatinine (safety pop.)

Parameter	Thal/Dex (n = 102)		Dex-alone (n = 102)	
	< 1.5 mg/dL	> 1.5 mg/dL	< 1.5 mg/dL	> 1.5 mg/dL
Constitutional	14/82 (17 %)	5/20 (25 %)	11/74 (15 %)	5/28 (18 %)
Neurology	22/82(27 %)	8/20 (40 %)	14/74 (19 %)	4/28 (14 %)
Gastrointestinal	13/82(16 %)	9/20 (45 %)	5/74 (7 %)	3/28 (11 %)
Cardiovascular	28/82 (34 %)	9/20/ (45 %)	14/74 (19 %)	16/28 (57 %)
Dermatology / Skin	2/82 (2 %)	3/20/ (15 %)	2/74 (3%)	3/28 (11 %)

Reviewer's Comment: In the Thal/Dex treatment arm, patients whose baseline serum creatinine was > 1.5 % appeared at somewhat higher risk of grade 3/4 toxicity in each of the five categories examined.

8.4 Pediatrics

The safety and efficacy of thalidomide in persons under age 18 have not been established. The Agency granted the Applicant a full waiver for pediatric studies in the original sNDA 21-430 submitted December 23, 2003 because MM is virtually non-existent in children. The youngest patients enrolled in studies ECOG E1A00, Mayo 98-80-13, and Thal MM-99-002 were age 37, 36 and 39 years, respectively.

8.5 Advisory Committee Meeting

This sNDA was not taken to an Advisory Committee.

8.6 Literature Review

I reviewed the published scientific and medical literature for clinical reports describing the use of thalidomide in MM. Sources included the Medline database using the search terms *multiple myeloma*, *drug therapy*, and *thalidomide*, as well as abstracts presented at recent meetings of the American Society of Hematology and American Society of Clinical Oncology.

Single-agent thalidomide in relapsed/refractory MM:

I identified 15 clinical studies that reported data on the efficacy of single-agent thalidomide in patients with relapsed/refractory MM. These 16 studies are summarized in Reviewer's Table 55.

Reviewer's Table 55: Studies of single-agent thalidomide in relapsed/refractory MM

Lead Author	Institution	Year Published
Alexanian ⁷⁴	MD Anderson Cancer Center, Houston, Texas	2000
Kneller ⁷⁵	Tel-Aviv University, Israel	2000
Juliusson ⁷⁶	University Hospital, Linkoping, Sweden	2000
Durie ^{77,78}	Cedars-Sinai, Los Angeles	2001
Hus ⁷⁹	Polish MM Study Group	2001
Bladé ⁸⁰	University of Barcelona	2001
Johnston ^{81,82}	Imperial College, London	2002
Neben ^{83,84}	University of Heidelberg, Germany	2002
Tosi, ⁸⁵	Italian Multicenter, Bologna	2002
Yakoub-Agha ^{86,87}	French Myeloma Intergroup	2003
Wechalekar ⁸⁸	University of Toronto, Canada	2003
Hoyer ⁸⁹	Heinrich-Hene University, Duesseldorf, Germany	2003
Kees ⁹⁰	University of Vienna, Austria	2003
Schey ⁹¹	United Kingdom Myeloma Forum	2003
Fenk ⁹²	University of Duesseldorf, Germany	2004

The designs of these 15 studies that reported efficacy data for single-agent thalidomide in relapsed/refractory MM are summarized in Reviewer's Table 56.

Reviewer's Table 56. Study designs for single-agent thalidomide in relapsed/refractory MM

Author*	Population	n	Study Design	Endpoints
Alexanian	Relapsed (n = 25) or refractory (n = 20) to chemotherapy. Five (11%) were post-transplant. Disease burden was not further defined.	45	Single-arm, dose escalation	Paraprotein response and toxicity
Kneller	Relapsing or resistant to a median of 3 prior lines of chemotherapy. Nine (53%) were post transplant. Mean baseline serum paraprotein 4.7 g/dL.	17	Single-arm, dose escalation	Paraprotein response and toxicity
Juliusson	Refractory to (n = 19) or relapsed after (n = 4) chemotherapy. Ten (43%) had undergone prior high-dose chemotherapy. Mean baseline serum paraprotein was 4.9 g/dL for IgG and 2.4	23	Single-arm, dose escalation	Paraprotein response, toxicity, and PFS

	g/dL for IgA.			
Durie	Relapsing or progressive MM following standard and/or high-dose chemotherapy	36	Single-arm, dose escalation only if lack of response	Paraprotein response, toxicity, EFS, and OS
Hus	Relapsed (n = 44) or refractory to (n = 9) a median of 4 prior lines of chemotherapy. Mean serum β_2M was 6.3 mg/L. Mean marrow plasma cells were 26%.	53	Multicenter, single-arm, dose escalation	Paraprotein response, toxicity, EFS, and OS
Bladé	Relapsed (n = 7) or refractory (n = 16) to a median of 2 prior lines of chemotherapy. Seven (30%) were post-transplant. Mean marrow plasma cells were 49%.	23	Single-arm, dose escalation	Paraprotein response and toxicity
Yakoub-Agha	Progression after ≥ 2 (median 3) lines of chemotherapy. Seventy percent were post-transplant. Serum β_2M was > 3 mg/L in 50 (42%).	83	Multicenter, single-arm, dose escalation	Paraprotein response, toxicity, EFS, and OS
Johnston	Poor response to > 2 regimens (n = 6), VAD-relapse (n = 4), VAD-refractory (n = 2); None had prior high-dose chemotherapy. Two had plasma cell leukemia.	12	Single-arm, dose escalation	Paraprotein response and toxicity
Neben	Relapsed by EBMT criteria after median 7 prior cycles of chemotherapy (number of regimens not specified). Sixty (70%) were post-transplant.	83	Single-arm, dose escalation	Paraprotein response, toxicity, PFS, and OS
Tosi	Relapsed or refractory by EBMT criteria to a median of 3 prior lines of chemotherapy. Twenty-six (37%) were post transplant. Sixty-one (94%) had stage III disease.	65	Multicenter, single-arm	Paraprotein response, toxicity, PFS, and OS
Wechalekar	Relapsed after a median of 3 prior lines of chemotherapy. Twenty two (73%) were post transplant. Five (17%) had del 13.	30	Single-arm, fixed dose	Paraprotein response and toxicity
Hoyer	First relapse after high dose chemotherapy. All patients had stage III disease, median β_2M 2.43 mg/L.	27	Single-arm	Paraprotein response, toxicity, and PFS
Kees	Relapsed or refractory disease (additional details not provided).	12	Single-arm	Paraprotein response, toxicity, and PFS
Schey	Relapsed or refractory to a median of 2 prior lines of chemotherapy. Twenty five (36%) were post-transplant. Median β_2M was 3.9 mg/L.	69	Multicenter, single-arm, dose escalation	Paraprotein response, toxicity, and PFS, and OS
Fenk	Relapsed after high-dose chemo-	32	Single arm,	EBMT response

	therapy. Median age was 55 years. Median β_2 M was 2.7 mg/dL.		dose escalation	
Total		610		

* Reference: please see Reviewer's Table 55

Reviewer's comments:

1. Each published clinical study evaluating the efficacy of thalidomide as a single agent in relapsed or refractory MM had a phase II, single-arm, open label design, without a control group.
2. Four of these studies were multiinstitutional.^{80,86-88,92} Five were conducted prospectively.^{78-80,84-86,92}
3. Only two studies⁸⁴⁻⁸⁶ defined the terms *refractory* and *progressive* in their eligibility criteria. Their authors defined *refractory* as < 25% paraprotein reduction in response to the last line of chemotherapy, and *progressive* as > 25% increase in paraprotein or other new disease manifestations.
4. Only one study⁷⁷ reported baseline serum and/or urine paraprotein levels.
5. The largest numbers of prior transplant recipients were enrolled by Hoyer, *et al.*, Neben, *et al.*, and the French Intergroup.
6. All 15 studies included serum or urine paraprotein responses and drug tolerability as primary endpoints. Four studies^{84,85,87-89,92,93} also calculated response duration and survival.
7. Two studies^{80,81,90} were reported in abstract form only, and thus lack supporting data (hemoglobin, calcium, etc.).

In 11 of these 15 studies, thalidomide was administered a single daily oral dose, usually at bedtime. Four studies^{77,80,81,87,88} used divided doses. Starting doses ranged from 50 mg daily^{78,79} to 400 mg daily,^{87,88} and the median starting dose was 200 mg.

In 9 studies, thalidomide was escalated as rapidly as tolerated to its MTD,^{75-77,80,81,84-88, 92} whereas 2 studies^{78,79,89} permitted escalation only if lower doses were ineffective. Rationales for the starting doses and escalation schedules selected were generally not provided.

Reviewer's Table 57: Dosing of single-agent thalidomide in relapsed/refractory MM

Author*	Initial Dose	Escalation	Highest Dose Achieved
Alexanian	200 mg at bedtime	200 mg/d q 2 weeks, up to 800 mg	"Few" tolerated 800 mg/d for > 4 weeks. "Some" tolerated 200 mg/d for < 2 months
Kneller	200 mg at bedtime	As tolerated, up to 800 mg	1 (6%) reached 200 mg/d 1 (6%) reached 400 mg/d 7 (41%) reached 600 mg/d 8 (47%) reached 800 mg/d
Juliusson	100 mg bid	100 mg bid weekly	3 (13%) not reported 5 (22%) reached 400 mg/d 12 (52%) reached 600 mg/d 3 (13%) reached 800 mg/d
Durie	50 mg at bedtime	100 mg/d q 2 weeks	11 (31%) reached 50 mg/d

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			14 (39%) reached 100 mg/d 7 (19%) reached 300 mg/d 4 (11%) reached 600 mg/d
Hus	100 mg bid	50 mg bid weekly	Not stated
Bladé	100 mg bid	100 or 200 mg/d q 2 weeks, up to 800 mg	5 (22%) reached 200 mg/d 6 (26%) reached 3-400 mg/d 6 (26%) reached 5-600 mg/d 6 (26%) reached 7-800 mg/d
Yakoub-Agha	50-800 mg daily (median 400) in 1,2, or 3 doses	50, 100, or 200 mg/d if tolerated	1 (1%) reached 50 mg/d 10 (12%) reached 100 mg/d 1 (1%) reached 150 mg/d 12 (14%) reached 200 mg/d 1 (1%) reached 250 mg/d 3 (4%) reached 300 mg/d 30 (36%) reached 400 mg/d 21 (25%) reached 600 mg/d 4 (5%) reached 800 mg/d
Johnston	50-100 mg at bedtime	Increased q 4weeks if tolerated <i>and</i> if no response	4 (33%) reached 100 mg/d 2 (17%) reached 150 mg/d 2 (17%) reached 200 mg/d 2 (17%) reached 300 mg/d 1 (8%) reached 400 mg/d 1 (8%) reached 500 mg/d
Neben	200 mg daily	200 mg/d q 2 weeks up to 800 mg	7 (8%) reached 200 mg/d 8 (10%) reached 300 mg/d 21 (26%) reached 400 mg/d 47 (56%) reached 800 mg/d
Tosi	100 mg daily	200 mg/d q 2 weeks up to 800 mg	5 (8%) not reported 11 (17%) reached 100 mg/d 4 (6%) reached 150 mg/d 18 (28%) reached 200 mg/d 6 (9%) reached 300 mg/d 4 (6%) reached 400 mg/d 3 (5%) reached 500 mg/d 12 (18%) reached 600 mg/d 2 (3%) reached 800 mg/d
Wechalekar	200 mg daily	None	21 (70%) continued 200 mg/d 4 (13%) reduced to 100 mg/d 5 (17%) discontinued therapy
Hoyer	Not stated	Not stated	Median dose of 200 mg; range 100-400 mg
Kees	Not stated	Not stated	Median dose of 100 mg; range 50-400 mg
Schey	200 mg daily	200 mg/d q 2wk up to 800 mg	Median dose of 300 mg; range 100-600 mg
Fenk	100 mg daily	Increased as tolerated	Median dose 200 mg; max. tolerated dose 400 mg

* Reference: please see Reviewer's Table 55

I reviewed these 15 published studies for information regarding the maximum thalidomide dose achieved by individual patients. My findings are summarized in Reviewer's Table 58.

Reviewer's Table 58: Max. doses of single-agent thalidomide achieved in rel./refr. MM

Maximum daily dose achieved (mg)	Patients	
	n	%
≤200	133	21.8
201-400	95	15.6
401-600	66	10.8
601-800	70	11.5
Not reported	246	40.3
Total	610	100.0

Reviewer's comments:

1. A total of 378 (62.0 %) patients reached at least 200 mg, 251 (41.1 %) reached at least 400 mg, and 165 (27.0 %) reached at least 600 mg. The maximum daily dose achieved was not reported for 246 (40.3 %) patients.
2. Levels of detail provided concerning thalidomide doses planned, achieved, and maintained varied considerably among these clinical trials. Three studies⁹¹⁻⁹³ did not report specific dosing schema. Neben, *et al.*, in contrast, reported detailed dosing information. Thalidomide in that study was escalated to 200, 300, and 400 mg in 100%, 92%, and 82% of patients, respectively, but 84% of patients eventually required dose reduction because of side effects.

The primary efficacy variables – paraprotein responses, PFS and OS – reported in these 16 studies are summarized in Reviewer's Table 58.

Reviewer's Table 59. Efficacy of single-agent thalidomide in relapsed/refractory MM

Author*	Paraprotein Response					PFS	OS
	>75%	50-75%	25-50%	SD	PD		
Alexanian	← 11 → (26%)		← 34 → (74%)			NR	NR
Kneller	5 (29%)	5 (29%)	1 (6%)	1 (6%)	5 (29%)	NR	NR
Juliusson	← 10 → (43%)		← 6 → (26%)		7 (30%)	NR	NR
Durie	6 (17%)	3 (8%)	7 (19%)	0	20 (56%)	NR	NR
Hus	7 (13%)	12 (23%)	8 (15%)	← 26 → (49%)		NR	250 weeks (median)
Bladé	← 3 → (13%)		9 (39%)	2 (9%)	9 (39%)	NR	NR
Yakoub-Agha	11 (13%)	29 (39%)	15 (18%)	← 28 → (34%)		50% (1-yr)	57% (1-yr)
Johnston	← 5 → (42%)			3 (25%)	4 (33%)	NR	NR

Neben	1 (1%)	16 (19%)	18 (21%)	← 48 → (59%)		45% (1 yr)	86% (1 yr)
Tosi	5 (8%)	12 (18%)	11 (17%)	← 37 → (57%)		NR	NR
Wechalekar	2 (6%)	7 (23%)	4 (14%)	2 (7%)	15 (50%)	NR	NR
Hoyer	1 (3%)	14 (54%)	3 (10%)	3 (10%)	6 (23%)	NR	NR
Kees	1 (8%)	3 (25%)	1 (8%)	3 (25%)	4 (33%)	NR	NR
Schey	7 (10%)	12 (17%)	15 (22%)	← 35 → (51%)		14 mo (med.)	19 mo (med.)
Fenk	19 (59%)		6 (19%)	6 (19%)	1 (3%)	23 mo (med.)	41 mo (med.)

* Reference: please see Reviewer's Table 55
NR = not reported

Paraprotein responses reported for the 610 patients in these 15 trials are pooled and summarized in Reviewer's Table 59. As reflected by the category "nonspecified nonresponder," a distinction often was not made between stable and progressive disease.

Reviewer's Table 60: Paraprotein response to single-agent thalidomide in rel./refr. MM

Paraprotein reduction	N (%)	95% CI
> 75%	46 (7.6 %)	(5.5, 9.6)
50-75%	156 (25.6 %)	(22.1, 29.0)
25-50%	103 (16.9 %)	(13.9, 19.9)
Stable disease	20 (3.3 %)	(1.9, 4.7)
Progressive disease	71 (11.6 %)	(9.1, 14.2)
Nonspecified nonresponders	214 (35.1 %)	(31.3, 38.9)
Total	610 (100)	

Reviewer's Comments:

1. Two hundred and two of the 610 patients (33.1%) in these 15 clinical studies attained a 50% paraprotein reduction. Rarely, however, did authors verify that second confirmatory samples were obtained (i.e. ≥ 8 weeks later to satisfy SWOG response criteria or ≥ 6 weeks later for EBMT response), and no trial reported IF data (required for CR^{EBMT}).
2. Reported response rates were reasonably consistent across the 15 studies. The proportion of patients whose paraprotein declined ≥ 75% ranged from 13%⁸² to 58%⁷⁵ and was ≥ 50% in one of the larger studies.^{88,89}
3. Neben, *et. al.*^{85,86} reported higher thalidomide doses to be associated with better response rates, tending to support the practice of escalating thalidomide to its MTD. Eighty-four percent of patients in that trial, however, required dose reduction. Five studies^{79,80,83,84,88-90,93} reported daily doses of 200 mg to be as effective as ≥ 600 mg.
4. No clinical trial has yet been designed to prospectively define a dose-response relationship or the optimal schedule to taper thalidomide following a response.
5. OS data, when reported, appear roughly comparable to those of relapsed and refractory MM patients receiving autologous stem cell transplantation⁹³ or bortezomib.⁹⁴ The Polish

MM Study Group reported unusually long OS for both thalidomide- and chemotherapy-treated patients. The reason for this relatively good outcome was not apparent.

Eleven of these 15 studies reported some AE data, as summarized Reviewer's Table 60. AE information was often limited to broad categories (e.g. neurological, dermatological, gastrointestinal) and grade was included rarely. Some authors mentioned toxicity only qualitatively (for example, Durie *et. al.* reported, "Low doses of thalidomide were generally well tolerated, but progressive peripheral neuropathy was a major long-term toxicity.").

I was also able to analyze toxicity data from an Australian Multicenter Study of 94 relapsed/refractory MM patients treated with thalidomide plus interferon- α because its authors reported toxicity data separately for the two drugs groups while combining efficacy data.⁹⁵ I excluded the study by Kees *et. al.* from Reviewer's Table 60 because its authors pooled AE data from patients receiving thalidomide monotherapy with those of patients receiving thalidomide-containing combination regimens.

Reviewer's Table 61: Toxicity of single-agent thalidomide in relapsed/refractory MM

Author*	AEs (n; %)		
	Neurologic	Dermatologic	Gastrointestinal
Kneller	1 (6 %) dose-limiting 11 (65 %) somnolence 5 (29 %) severe tiredness 1 (6 %) dizziness	None	5 (29 %) constipation
Juliusson	23 (100 %) mild sedation	1 (4 %) dose limiting 3 (13 %) leg edema	Moderate obstipation
Yakoub-Agha	56 (67 %) somnolence 10 (12 %) neuropathy 14 (17 %) mood change	15 (18 %) edema	45 (54 %) constipation 9 (11 %) xerostomia 8 (10 %) nausea/vomit
Bladé	16 (70 %) somnolence 11 (48 %) fatigue 6 (26 %) tremor 3 (13 %) paresthesias 3 (13 %) dizziness 1 (4 %) headache 1 (4 %) ataxia	3 (13 %) rash 2 (9 %) edema	14 (61 %) constipation
Johnston	4 (36%) somnolence, dose-limiting in one case	None	None
Neben	Grade 1-2 42 (51 %) somnolence 30 (36 %) paresthesias 30 (36 %) weakness 27 (33 %) tremor 20 (24 %) dizziness Grade 3-4 5 (6 %) paresthesias	12 (14 %) rash	35 (42 %) dry mouth 40 (48 %) constipation
Tosi	22 (34 %) lethargy 9 (24 %) "neurological"	7 (11 %) rash 3 (3 %) edema	34 (52 %) constipation

Wechalekar	16 (54 %) fatigue 14 (48 %) sleepiness 7 (24 %) neuropathy 3 (10 %) dizziness	2 (8 %) rash 2 (8 %) dryness	13 (43 %) constipation
Hoyer	Grade 1-2 17 (58 %) neuropathy 4 (13 %) fatigue	None	Grade 1-2 11 (39 %) constipation
Schey	Grade 1-2 22 (32 %) neuropathy 16 (23 %) lethargy 3 (4 %) dizziness 1 (2 %) confusion 1 (2 %) depression 1 (2 %) insomnia 1 (2 %) tremor Grade 3-4 3 (4 %) dizziness 1 (2 %) neuropathy	Grade 1-2 5 (7 %) rash Grade 3-4 1 (2 %) rash	Grade 1-2 5 (7 %) constipation Grade 3-4 2 (3 %) constipation
Mileshkin	Grade 1-2 9 (12 %) headache 50 (67 %) fatigue 14 (19 %) depressed level of consciousness 47 (63 %) neuropathy 9 (12 %) dizziness Grade 3 6 (8 %) fatigue 2 (3 %) depressed level of consciousness 10 (13 %) neuropathy	Grade 1-2 11 (15 %) rash Grade 3 2 (3 %) rash	Grade 1-2 12 (16 %) nausea 46 (61 %) constipation 10 (13 %) dry mouth Grade 3 10 (13 %) constipation

* Reference: please see Reviewer's Table 55

In addition to the AEs categorized above, the following miscellaneous AEs were reported:

- Kneller *et. al.*
1 (6 %) bradycardia
- Juliusson *et. al.*
2 (9 %) pneumonia
- Yakoub-Agha, *et. al.*
19 (23 %) "others"
- Neben, *et. al.*
20 (24 %) grade 1-2 infection
7 (8 %) grade 3-4 infection
3 (4 %) deep venous thrombosis
2 (2 %) syncope
10 (12 %) mood change
3 (3 %) exacerbation of heart failure

- 1 (1 %) hearing disturbance
- 1 (1 %) leukopenia
- Bladé *et. al.*
 - 1 (4 %) renal failure with nephrotoxic antibiotic
 - 2 (9 %) tachycardia
 - 1 (4 %) atrioventricular block
 - 1 (4 %) cardiac arrest
- Schey, *et. al.*
 - 7 (10 %) thromboembolic complications (2 pulmonary emboli, 1 stroke, and 3 transient ischemic attacks)
 - 2 (3 %) infection
 - 2 (3 %) hemorrhage
 - 1 (2 %) thrombocytopenia
- Tosi, *et. al.*
 - 3 (5 %) renal toxicity
 - 2 (3 %) leukopenia
 - 1 (1 %) deep venous thrombosis
 - 3 (5 %) other
- Welacher, *et. al.*
 - 1 (2 %) blurring vision
 - 1 (2 %) chin numbness
 - 1 (2 %) cracked feet
 - 1 (2 %) oral vesicles
- Mileshkin, *et. al.*
 - 1 (5 %) anemia
 - 6 (31 %) neutropenia

Thalidomide as treatment for newly diagnosed MM:

No clinical study has, to my knowledge, evaluated thalidomide as single-agent therapy for patients with newly diagnosed MM. I identified 7 studies that evaluated the combination of Thal/Dex in this setting, and these are summarized in Reviewer’s Table 62. The use of thalidomide as part of other combination chemotherapy regimens is beyond the scope of this review.

Reviewer’s Table 62: Studies of Thal/Dex in newly diagnosed MM

Lead Author	Institution	Year Published
Rajkumar ^{96,97}	Mayo Clinic, Rochester, MN	2002
Weber ⁹⁸	MD Anderson Cancer Center, Houston, Texas	2003
Wang ⁹⁹	MD Anderson Cancer Center, Houston, Texas	2005
Abdelkefi ¹⁰⁰	Centre National de Greffe de Moelle Osseuse, Tunis, Tunisia	2005
Cavo ¹⁰¹	Institute of Hematology and Medical Oncology Seragnoli, Bologna, Italy	2005
Ludwig ¹⁰²	1st Department of Medicine and Oncology, Wilhelminenspital, Vienna, Austria	2005*

Clueppelberg ¹⁰³	Not stated	2005*
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* abstract only

The designs of these 7 studies reporting efficacy data for Thal/Dex in newly diagnosed MM are summarized in Reviewer's Table 63.

Reviewer's Table 63. Study designs for Thal/Dex in newly diagnosed MM

Author*	Population	N	Study Design	Endpoints
Rajkumar	BM plasma cells > 10 % and serum paraprotein > 2 g/dL or urine paraprotein > 400 mg/24 h	50	Single-arm, fixed dose (200 mg/d thalidomide)	Paraprotein response, stem cell transplant at 4 mo
Weber	Symptomatic MM	40	Single-arm, fixed dose (max 400 mg/d thalidomide)	Paraprotein response, toxicity
Wang	Hb < 8.5 g/dl and/or Ca ⁺⁺ > 11.5 mg/dL	26	Single-arm, limited (up to 300 mg/d) dose-escalation	Paraprotein response, toxicity, stem cell transplant at 2 mo
Abdelkefi	Age < 61 years, Durie-Salmon stage II or III, BM plasma cells > 10 %, and serum paraprotein > 2 g/dL or urine paraprotein > 400 mg/24 h	60	Single-arm, fixed-dose (200 mg/d) thalidomide	EBMT response, toxicity, stem cell transplant at 2 mo
Cavo	Symptomatic MM	100	Retrospective case-control analysis, low-dose (100-200 mg/d) thalidomide	EBMT response, toxicity, stem cell transplant at 4 mo
Ludwig	Not otherwise specified	72 [†]	Randomized Thal/Dex versus MP	Response, time to response, toxicity
Clueppelberg	Not otherwise specified	29	Single-arm, fixed dose (100 mg/d thalidomide)	Response, time to response, toxicity
Total		363		

* Reference: please see Reviewer's Table 62

[†] Thal/Dex treatment arm only (72 evaluable for toxicity and 58 for response)

Reviewer's Comments:

1. The most frequent use of Thal/Dex in previously untreated MM patients has been as a bridge to stem cell transplantation.
2. Few investigators have attempted to increase the dose of thalidomide in this setting above 200 mg daily. Rajkumar, *et. al.* found higher thalidomide doses to be associated with unexpected skin toxicity, and amended the protocol after the first 7 patients to fix the dose at 200 mg/d.

The primary efficacy variables reported in these 7 studies are summarized in Reviewer's Table 64.

Reviewer's Table 64. Efficacy of Thal/Dex in newly diagnosed MM

	Paraprotein Response	
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Author*	>75%	50-75%	25-50%	SD	PD	Follow-up
Rajkumar	26 (52 %)	8 (16 %)	12 (24 %)	← 4 → (8 %)		31 (62 %) proceeded to stem cell collection; TTP among the other 24 patients was 21 months
Weber	5 (16 %)	5 (16 %)	19 (48 %)	11 (28 %)		21 (52 %) proceeded to stem cell collection
Wang	19 (73 %)	← 7 → (27 %)				Median PFS > 25 months and OS > 30 months
Abdelkefi	14 (24 %)	30 (50 %)	6 (10 %)	7 (12 %)	3 (5 %)	58 (96 %) proceeded to stem cell mobilization
Cavo	19 (19 %)	57 (57 %)	← 24 → (24 %)			83 (83 %) proceeded to mobilization of $\geq 4 \times 10^6$ CD34 ⁺ cells
Ludwig	13 (22 %)	18 (32 %)	11 (19 %)	5 (9 %)	11 (19 %)	Not reported
Klueppelberg	← 18 → (62 %)		8 (28 %)	← 3 → (10 %)		Not reported

* Reference: please see Reviewer's Table 62

Paraprotein responses reported for the 363 patients in these 7 studies are pooled and summarized in Reviewer's Table 65.

Reviewer's Table 65: Paraprotein response to Thal/Dex in newly diagnosed MM

Maximum daily dose achieved (mg)	Patients	
	n (%)	95 % CI
> 75 %	96 (26.4)	(21.9, 31.0)
50 - 75 %	136 (37.5)	(32.5, 42.5)
25 - 50 %	56 (15.4)	(11.7, 19.1)
Stable disease	12 (3.3)	(1.5, 5.2)
Progressive disease	14 (3.9)	(1.9, 5.8)
Nonspecified nonresponders	49 (13.5)	(10.0, 17.0)
Total	363 (100)	

Reviewer's Comment: Published literature suggests that paraprotein responses of > 50 %, 50-75%, and > 75% are all more likely when Thal/Dex is used in newly diagnosed MM than when thalidomide-alone is used in relapsed/refractory MM.

Reviewer's Table 66: Toxicity of Thal/Dex in newly diagnosed MM

Author*	AEs (n; %)		
	Neurologic	Dermatologic	Gastrointestinal
Rajkumar	Grade 3-4 1 (2 %) sedation 1 (2 %) depression 1 (2 %) neuropathy	Grade 3-4 4 (8 %) rash	Grade 3-4 4 (8 %) constipation
Weber	All grades 20 (50 %) paresthesias 5 (13 %) unsteadiness	All grades 22 (55 %) rash/dry skin	All grades 22 (55 %) constipation

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	12 (30 %) tremors 22 (55 %) fatigue		
Wang	Grade 1-2 15 (58 %) fatigue 2 (8 %) neuropathy Grade 3-4 1 (4 %) fatigue 1 (4 %) neuropathy	Grade 1-2 2 (8 %) rash	Grade 1-2 9 (35 %) constipation Grade 3-4 1 (4 %) nausea
Abdelkefi	Grade 3-4 None	Grade 3-4 3 (5 %) neuropathy	Grade 3-4 3 (5 %) constipation
Cavo	Grade 3-4 None	Grade 3-4 4 (4 %) neuropathy	Grade 3-4 9 (9 %) constipation
Ludwig	Grade 2-4 Fatigue (48 %) Neuropathy (22 %) Psychological (19 %)	Grade 2-4 skin 10 %	Grade 2-4 28 % constipation

* Reference: please see Reviewer's Table 62

In addition to the AEs categorized above, the following miscellaneous grade 3-4 AEs were reported:

- Rajkumar, *et. al.*
6 (12 %) VTE
2 (4 %) dyspnea
1 (2 %) arrhythmia
1 (2 %) inner ear
1 (2 %) syncope
- Weber, *et. al.*
14 (35 %) edema
5 (13 %) infections
6 (15 %) VTE
- Abdelkefi, *et. al.*
7 (12 %) infection
- Cavo, *et. al.*
15 (15 %) VTE
4 (4 %) infection
- Ludwig
13 (18 %) VTE.

Reviewer's Comment: In four of the studies evaluating Thal/Dex for newly diagnosed MM,^{100,102,103,105} the authors observed clusters of VTE among patients accrued early. These four protocols were therefore amended to include prophylactic anticoagulation with heparin or warfarin, and no further VTE were observed after those amendments.

Five AEs – sedation, constipation, peripheral neuropathy, rash, and VTE – have been described in published literature as being associated with thalidomide. These five AEs are discussed in detail below.

1. Sedation

Most patients receiving thalidomide for MM appear to experience at least mild sedation. Although sedation is somewhat mitigated by bedtime dosing, and tolerance often develops, this symptom is dose-limiting in about a third of cases.^{104,105}

2. Constipation

Most MM patients who take thalidomide experience at least some constipation. This problem is usually manageable with a daily cathartic regimen, and is seldom dose-limiting.

3. Peripheral neuropathy

Neuropathy or symptoms potentially attributable to neuropathy (e.g. paresthesias, tremor, weakness) are reported by up to 80 % of patients in the literature evaluating single-agent thalidomide for relapsed or refractory MM or Thal/Dex for newly diagnosed MM, and was a principal DLT. Initial symptoms are typically symmetrical distal paresthesias, beginning within a few months and progressing centripetally. Tendon reflexes are usually unaffected or depressed, but can be increased. Weakness is a late finding.¹⁰⁶ The largest prospective study of thalidomide neuropathy involved doses lower than usually prescribed for MM and is therefore not applicable to this clinical setting.¹⁰⁷

Clinical and electrophysiologic data on thalidomide neuropathy were collected prospectively in a cohort of patients receiving thalidomide at either a fixed dose of 200 mg/day (low-dose arm) or initially at 200 mg/day and increased to a maximum daily dose of 1200 mg (dose-escalation arm) for hormone-refractory prostate cancer. Fifty-four patients were enrolled in the low-dose arm and 13 in the dose-escalation arm. No other drugs with known or suspected neuropathic side effects were administered during the period of study. Thirty-five patients had symptoms or signs of peripheral neuropathy at baseline. Six of 8 patients treated for at least 6 months had neuropathic symptoms and electrophysiologic abnormalities, and by 9 months, all 3 patients who continued in the trial had developed neuropathy.^{108,109}

Small cases series from the dermatologic literature have reported that the most sensitive parameter for detecting thalidomide-induced polyneuropathy is electrophysiologic measurement of the sensory nerve action potential amplitude (SNAP). The characteristic finding is decreased SNAP amplitude, consistent with demyelination. Thermal thresholds are not altered, indicating that thin myelinated and unmyelinated axons are spared.¹¹⁰ At Johns Hopkins University, sural nerve biopsies were performed on 3 of 7 patients with clinical and electrophysiologic evidence of thalidomide-induced peripheral neuropathy, and all 3 had axonal degeneration.¹¹¹ Some authors suggest that NCS at baseline and serially during therapy, as a supplement to patient self-reporting of symptoms and physical examination, might be useful to help guide decisions about tapering and discontinuing therapy.^{112,113} This hypothesis has not been studied prospectively.

In summary, the relation between peak and cumulative thalidomide doses to the risk, severity, and reversibility of peripheral neuropathy vary among published reports. Grade 1-2 neuropathy often improved following dose reduction or interruption, whereas doses ≥ 400 mg/d tended to be associated with higher grade neuropathy that was less readily reversible.

4. VTE

VTE is, along with polyneuropathy, a serious complication of thalidomide in MM. I identified several clinical reports describing this association. The magnitude of risk in those studies not employing prophylactic anticoagulation is summarized in Reviewer's Table 73.

Reviewer's Table 67. Incidence of VTE during thalidomide for MM

Regimen and author	Disease Status	VTE (%)
Thalidomide alone		
Barlogie ⁴⁴	Relapsed/refractory	<5
Arnulf ¹¹⁴	Relapsed/refractory	5
Rajkumar ¹¹⁵	Newly diagnosed	3
Weber ¹¹⁶	Newly diagnosed	4
Thalidomide and dexamethasone		
Weber ¹¹⁹	Newly diagnosed	15
Dimopoulos ¹¹⁷	Relapsed/refractory	7
Anagnostopoulos ¹¹⁸	Relapsed/refractory	8
Zangari ¹¹⁹	Relapsed/refractory	2.5
Rajkumar ¹²⁰	Newly diagnosed	14
Thalidomide, melphalan, and prednisone		
Palumbo ¹²¹	Newly diagnosed	19
Thalidomide, dexamethasone, and doxorubicin		
Kropff ¹²²	Relapsed/refractory	8
Zangari ¹²²	Relapsed/refractory	16
Arnulf ¹¹⁷	Relapsed/refractory	28
Osman ¹²³	Newly diagnosed	27
Zangari ¹²⁴	Newly diagnosed	28
Zervas ¹²⁵	Newly diagnosed	10

Reviewer's comments:

1. The reported risk of VTE ranges from approximately 3 % to 5 % when thalidomide is used alone, reaches up to 8 % when thalidomide is combined with dexamethasone, and ranges from 8 % to 28 % when thalidomide was used in combination with standard chemotherapeutic agents such as alkylating agents or anthracyclines.
2. The causality determination for thromboembolic events is especially difficult in cancer patients who may have multiple other underlying conditions which would predispose them to develop a VTE. For example, postulated thrombogenic mechanisms in MM include paraprotein interference with fibrin function, procoagulant autoantibodies, inflammatory cytokines actions on endothelium, acquired activated protein C resistance,

adhesion molecule upregulation, and direct endothelial injury or secretion of thrombogenic and angiogenic substances.¹²⁶

3. Most VTE's reported above were lower extremity deep venous thrombosis and pulmonary emboli. This reviewer did not find evidence linking thalidomide use in MM to VTE in unusual sites (mesenteric, retinal, etc.).

4. VTE has also been reported during thalidomide use in non-Hodgkin's lymphoma¹²⁷ renal cell carcinoma,¹²⁸ and myelodysplasia.¹²⁹

Five of the 6 studies listed in Reviewer's Table 71 as having evaluated thalidomide plus dexamethasone for patients newly diagnosed MM incorporated antiplatelet therapy or anticoagulation during at least a portion of the protocol. In four of those studies, relatively high rates of VTE were noted early, the protocols were subsequently amended to include prophylactic anticoagulation, and rates of VTE thereafter appeared lower. These data are summarized in Reviewer's Table 74.

Reviewer's Table 68: VTE rate with Thal/Dex in newly diagnosed MM

Author*	Prophylactic Antithrombotic Therapy	VTE Rate
Rajkumar	None	6 (12 %)
Weber		
First 24 patients	Warfarin (1 mg/d)	6 (15 %)
Subsequent 16 patients	Warfarin (target INR 2-3) or LMW heparin	0
Wang	Warfarin (target INR 2-3) or heparin	2 (8 %)
Abdelkefi		
First 13 patients	None	2 (15 %)
Subsequent 47 patients	Warfarin (target INR 2-3) or LMW heparin	0
Cavo		
First 19 patients	None	5 (26 %)
Subsequent 81 patients	Warfarin (1.25 mg/d)	10 (12 %)
Ludwig		
Thal/Dex treatment arm	None	4 (8 %)
Melphalan/prednisone arm	None	2 (4 %)
Klueppelberg		
First 36 patients	None	6 (18 %)
Subsequent patients	Aspirin (81 mg/d)	Not reported

* Reference: please see Reviewer's Table 68

Reviewer's Comment: Prophylactic anticoagulation prescribed in conjunction with thalidomide may lessen the potential for VTE.

5. Rash

The most detailed account of thalidomide-related skin reactions in MM patients was published by the Mayo Clinic Department of Dermatology. Among 87 myeloma patients in an open-label trial of thalidomide with or without dexamethasone, minor to moderate rash (morbilliform, seborrheic, maculopapular, or nonspecific dermatitis) developed in 46 % of those taking thalidomide alone and in 43 % of those taking thalidomide and dexamethasone. Severe reactions (exfoliative erythroderma, erythema multiforme, or toxic epidermal necrolysis) requiring

hospitalization and drug withdrawal occurred in 3 patients receiving thalidomide and dexamethasone.¹³⁰

Adverse Events in Published Case Reports

Please see my previous review for a comprehensive listing of published AEs. Since that review, reports of one additional case of pulmonary hypertension and one case of reversible interstitial pneumonitis were published.^{131,132}

Reviewer's comment: The AEs described in these case reports were not definitively attributed to thalidomide.

8.7 Postmarketing Risk Management Plan

Thalidomide will continue to be distributed under the restricted S.T.E.P.S.[®] program

8.8 Other Relevant Materials

None

9 OVERALL ASSESSMENT

9.1 Conclusions

The Applicant submitted primary data from one multicenter, open-label, randomized clinical trial and two small, single-arm studies evaluating the use of thalidomide in MM. These three registration studies differed in design, patient population, and treatment regimen. Data from these studies were compared against those from published literature. They support the conclusion that thalidomide has activity in MM.

A limitation common to each of the three registration studies was that response criteria used were less stringent than those recommended by other groups. Other limitations were that response data and AE monitoring were relatively incomplete, and no evidence of symptomatic improvement was provided. Despite these limitations, studies Mayo 98-80-13 and Thal MM-99-002 suggest that thalidomide has modest single-agent activity on the order of 13% in the relapsed/refractory disease setting. Response rates based on a serum or urine paraprotein response resulted in a statistically significant difference in favor of the combination arm (46.6 % compared with 27.9 %) for dexamethasone alone; $p = 0.003$). In response to the review team's queries regarding the data, Celgene submitted additional information on November 1 and informed the review team that additional data is forthcoming. After review of all new data and reanalysis, if the application's results continue to show a statistically significant difference in favor of the thalidomide combination for best response within the first 4 cycles, thalidomide may be given accelerated approval (AA) for the treatment of newly diagnosed patients with multiple myeloma.

Study ECOG E1A00 was not designed or powered to detect an OS difference, and OS was similar in both treatment groups (75.4 weeks for Thal/Dex versus 76.6 weeks for dexamethasone-alone). Conclusions about PFS and OS can not be drawn from Mayo 98-80-13 or Thal MM-99-002 because they were each small, single-arm studies.

Most patients in Study E1A00 experienced at least one grade 3-4 AE (84.3 % on the Thal/Dex treatment arm, and 73.5 % on the dexamethasone-alone arm). The reported incidence of grade 3-4 AEs was lower in Studies Mayo 98-80-13 and Thal MM-99-002, possibly because differing data collection techniques. The most common toxicities with thalidomide, somnolence, constipation, neuropathy, VTE, and rash, have been previously described.

Data from Trial E1A00 indicate that the risk of VTE is significantly higher in patients concurrently receiving dexamethasone, and the thalidomide label should be updated accordingly. None of the three registration studies were designed to evaluate the reversibility of thalidomide-induced neuropathy.

I also searched existing published medical literature, and found 15 open-label, phase II studies that evaluated the safety and efficacy of thalidomide in a total of 610 patients with relapsed or refractory MM plus seven open-label, phase II studies that evaluated thalidomide in combination with dexamethasone in 363 total patients with newly diagnosed MM. Data from these studies suggest that single-agent thalidomide induces an overall rate of paraprotein response, defined as a single (unconfirmed) $\geq 50\%$ reduction, of 33 % in relapsed/refractory MM and 64 % in combination with dexamethasone in newly diagnosed MM.

I reviewed the published medical literature regarding the risk of VTE during thalidomide treatment for MM and identified several relevant clinical reports. The reported risk of VTE ranges from approximately 3 % to 5 % when thalidomide is used alone, reaches up to 8 % when thalidomide is combined with dexamethasone, and ranges from 8 % to 28 % when thalidomide was used in combination with standard chemotherapeutic agents such as alkylating agents or anthracyclines.^{42,80-91} The higher rate of VTE in Study E1A00 reported in the Thal/Dex treatment arm (22.5 %) than among patients who received dexamethasone-alone (4.9 %), consistent with this literature. The causality determination for such events is especially difficult in cancer patients in whom multiple confounding variables may be present.

Prophylactic anticoagulation prescribed in conjunction with thalidomide may lessen the potential for VTE. Amendments to recent clinical trial designs suggest that this practice has become common in the academic community. However, these therapies are not without risk to patients. Anticoagulation for prophylaxis has been associated with severe and fatal bleeding (as outlined in the warfarin labeling). MM patients can be at increased risk for both bleeding and thrombotic complications because of acquired bleeding and clotting disorders. MM patients are also at risk for falls and pathologic fractures which can become complicated by bleeding. Therefore, the decision to take prophylactic measures should be done carefully after an assessment of an individual patient's underlying risk factors.

9.2 Recommendation on Regulatory Action

This reviewer recommends taking an approvable action on thalidomide for patients with MM. The risk-benefit ratio potentially favors the eventual approval of thalidomide for this indication. This indication could increase the available options for therapy of patients this disease.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No new recommendations.

9.3.2 Required Phase 4 Commitments

Please see Section 1.2.2 of this review.

9.3.3 Other Phase 4 Requests

Please see Section 1.2.3 of this review.

9.4 Labeling Review

The review team's proposed labeling will include revisions to the indications and precautions sections.

9.5 Comments to Applicant

None

Appears This Way
On Original

Clinical Review
Michael Brave, M.D.
sNDA 21-430
Thalidomide (Thalomid)

10 APPENDICES

None

Appears This Way
On Original

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