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APPLICATION NUMBER:

211379Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Application Number(s)	211379
Priority or Standard	Standard
Submit Date(s)	September 6, 2018
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Division / Office	Division of Hematology Products/Office of Hematology and Oncology Products
Reviewer Name(s)	Rachel Ershler, MD
Clinical Team Leader	Nicole Gormley, MD
Review Completion Date	September 20, 2019
Established Name	Dexamethasone
(Proposed) Trade Name	HEMADY
Therapeutic Class	Corticosteroid
Applicant	Dexcel Pharmaceutics
Formulation(s)	Immediate Release Tablet (20 mg)
Dosing Regimen	20 mg or 40 mg daily in combination with other listed anti-myeloma drugs.
Indication(s)	In combination with other anti-myeloma products for the treatment of adults with multiple myeloma.

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Table 1: List of Abbreviations

ALT	Alanine aminotransferase
ANDA	Abbreviated New Drug Application
ASCT	Autologous stem-cell transplantation therapy
AST	aspartate aminotransferase
BA	Bioavailability
BE	bioequivalence
BLA	Biologics License Application
CLcr	creatinine clearance
CR	complete response
CTD	cyclophosphamide-thalidomide-dexamethasone
DOR	duration of response
DPT	Dexcel Pharma Technologies
EBMT	European Group for Blood and Bone Marrow Transplant
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GR	Glucocorticoid receptor
HR	hazard ratio
IQR	Interquartile range
i.v.	Intravenous
IMWG	International Myeloma Working Group
IND	Investigational New Drug
iPSP	initial Pediatric Study Plan
IRAC	Independent Review Adjudication Committee
IRC	Independent Review Committee
ISE	Integrated Summary of Effectiveness
ISS	Integrated Summary of Safety
ITT	Intent-to-treat
Kd	carfilzomib - dexamethasone

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends regular approval for HEMADY (dexamethasone) for the indication, "In combination with other anti-myeloma products for the treatment of adults with multiple myeloma".

No new clinical data were submitted for this NDA. The basis for regular approval of this 505(b)(2) application for dexamethasone includes the following:

1. Clinical pharmacology study in healthy volunteers to establish the scientific bridge between the proposed HEMADY 20 mg tablet and West-Ward's dexamethasone 4 mg tablet (ANDA 084612).
2. The previous findings of safety and efficacy for the following listed drugs:
   - Decadron (dexamethasone, NDA 011664)[1] Tablets 0.25 mg, 0.5 mg, 0.75 mg, 1.5 mg, 4 mg and 6 mg
   - Thalomid (thalidomide) Capsules (NDA 020785)[2]
   - Revlimid (lenalidomide) (NDA 021880)[3]
   - Velcade (bortezomib) Injection (NDA 021602)[4]
   - Pomalyst (pomalidomide) (NDA 204026)[5]
   - Farydak (panobinostat) (NDA 205353)[6]
   - Ninlaro (ixazomib) (NDA 208462)[7]
   - Kyprolis (carfilzomib) (NDA 202714)[8]
3. Published literature describing the results of clinical studies using dexamethasone in combination with these anti-myeloma drugs.

1.2 Risk Benefit Assessment

In order to support the proposed indication, the Applicant is relying on the FDA's findings of safety and efficacy for Decadron, Thalomid, Velcade, Revlimid, Pomalyst, Ninlaro, Farydak and Kyprolis, as well as the published literature describing the results of clinical studies using dexamethasone in combination with these anti-myeloma drugs. Refer to the approved labeling for these anti-myeloma drugs for the risk/benefit analyses for the listed drugs.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable

1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: Dexamethasone

Trade Name: HEMADY

Drug Class: Corticosteroid

Proposed Indication: In combination with other anti-myeloma products for the treatment of adults with multiple myeloma.

Proposed Dosage and Administration: 20 mg or 40 mg orally daily on specific days of treatment cycle in combination with other anti-myeloma drugs. Specific dosing regimens are included in the prescribing information of each of the listed anti-myeloma drugs. HEMADY can be taken with or without food.

Table 2: Dexamethasone Dosing Regimen for Listed Anti-Myeloma Drugs

Drug	Dexamethasone Dosing Regimen for Multiple Myeloma (MM)
Thalomid (thalidomide) NDA 020785	**MM, Td**: 40 mg/day on days 1-4, 9-12, and 17-20 every 28 days
Velcade (bortezomib) NDA 021602	**Relapsed MM, Vd:** After four cycles, 20 mg orally daily on the day of and after VELCADE administration **Retreatment of Relapsed MM, Vd:** With VELCADE in Cycle 1, with an additional 11 patients receiving dexamethasone during the course of VELCADE retreatment cycles
Revlimid (lenalidomide) NDA 21880	**MM, Rd Continuous and Rd18 arms (25 mg R QD D1-21):** 40 mg (20 mg > 75 years) once daily on Days 1, 8, 15, and 22 of each 28-day cycle **MM with ≥1 therapy, Rd (25 mg R QD D1-21):** 40 mg orally QD on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles and 40 mg orally QD on Days 1 to 4 of each 28-day cycle after the first 4 cycles of therapy.
Pomalyst (pomalidomide) NDA 204026	**MM, Pd:** **Low-dose:** 40 mg (20 mg if >75 years) daily on Days 1, 8, 15, and 22 of each 28-day cycle **High-dose:** 40 mg (20 mg if >75 years) daily on Days 1 to 4, 9 to 12, and 17 to 20 of a 28- day cycle
Ninlaro (ixazomib) NDA 208462	**NRd:** 40 mg on Days 1, 8, 15, and 22 of a 28-day cycle
Farydak (panobinostat) NDA 205353	**FVd (C1-8):** 20 mg orally 1, 2, 4, 5, 8, 9, 11, 12 of 21-day cycle **FVd (C9-16):** 20 mg orally 1, 2, 8, 9 of 21-day cycle

Kyprolis (carfilzomib) NDA 202714	**Kd 20/70:**40 mg orally or IV on Days 1, 8, and 15 of all cycles and on Day 22 of Cycles 1 to 9 **Kd 20/56:** 20 mg orally or IV on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day cycle **KRd 20/27:** 40 mg by orally or IV on Days 1, 8, 15, and 22 of the 28-day cycles

d=dexamethasone, T=Thalomid, V=Velcade, R=Revlimid, P=Pomalyst, N=Ninlaro, F=Farydak, K=Kyprolis
Source: Based on Thalomid, Velcade, Revlimid, Pomalyst, Ninlaro, Farydak, and Kyprolis labeling

Contraindications:

- Hypersensitivity to dexamethasone
- Systemic fungal infections

2.3 Availability of Proposed Active Ingredient in the United States

Dexamethasone is a synthetic steroidal glucocorticoid that first approved on October 30, 1958 (Decadron, NDA 011664). Decadron was withdrawn from the market in 2007. Several generic versions of Decadron tablets are currently approved including, West-Ward's dexamethasone tablets, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg (ANDAs: 084611, 084613, 084610, 087916, 084612, 088306 and 088316).

Dexamethasone is currently approved for the following indications:

1. *Allergic states:* control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reactions, perennial or seasonal allergic rhinitis, and serum sickness.
2. *Dermatologic diseases:* bullous dermatitis herpetiformis, exfoliative erythroderma, mycosis fungoides, pemphigus, and severe erythema multiforme (Stevens-Johnson syndrome).
3. *Endocrine disorders:* Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; may be used in conjunction with synthetic mineralocorticoid analogs where applicable; in infancy mineralocorticoid supplementation is of particular importance), congenital adrenal hyperplasia, hypercalcemia associated with cancer, and nonsuppurative thyroiditis.
4. *Gastrointestinal diseases:* To tide the patient over a critical period of the disease in regional enteritis and ulcerative colitis.
5. *Hematologic disorders:* Acquired (autoimmune) hemolytic anemia, congenital (erythroid) hypoplastic anemia (Diamond-Blackfan anemia), idiopathic thrombocytopenic purpura in adults, pure red cell aplasia, and selected cases of secondary thrombocytopenia.
6. *Miscellaneous:* Diagnostic testing of adrenocortical hyperfunction, trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block when used with appropriate antituberculous chemotherapy.
7. *Neoplastic diseases:* For the palliative management of leukemias and lymphomas.

8. *Nervous system:* Acute exacerbations of multiple sclerosis, cerebral edema associated with primary or metastatic brain tumor, craniotomy or head injury.
9. *Ophthalmic diseases:* Sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids.
10. *Renal diseases:* To induce a diuresis or remission of proteinuria in idiopathic nephrotic syndrome or that due to lupus erythematosus.
11. *Respiratory diseases:* Berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, idiopathic eosinophilic pneumonias, symptomatic sarcoidosis.
12. *Rheumatic disorders:* As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis, acute rheumatic carditis, ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy). For the treatment of dermatomyositis, polymyositis, and systemic lupus erythematosus.

Dexamethasone for Multiple Myeloma

Dexamethasone is not currently approved for use in multiple myeloma specifically. The dexamethasone label does include an indication for neoplastic conditions. However, dexamethasone has been routinely used for the treatment of multiple myeloma for over 30 years and has been included as part of the backbone regimen for numerous FDA-approved anti-myeloma therapies.[9,10] Dexamethasone is also included in multiple treatment protocols in the national comprehensive cancer network (NCCN) guidelines for multiple myeloma.[11] Evidence suggests that dexamethasone inhibits proliferation and induces apoptosis in multiple myeloma cells in a dose dependent manner. This anti-myeloma effect is mediated via the glucocorticoid receptor (GR) and was confirmed in both multiple myeloma cells obtained from patients, as well as in well-established multiple myeloma cell lines.[12] The safety and efficacy of dexamethasone in combination with anti-myeloma drugs is well established.

2.4 Important Safety Issues With Consideration to Related Drugs

The Decadron label contains warnings and precautions for the following:

- Alternations in endocrine function
- Immunosuppression and increased risk of infections
- Alteration in cardiovascular/renal function
- Venous and arterial thromboembolism
- Vaccination
- Ophthalmic effects
- Gastrointestinal perforation
- Osteoporosis
- Behavioral and Mood disturbances

- Kaposi's Sarcoma
- Embryo-Fetal toxicity

See prescribing information for Thalomid, Velcade, Revlimid, Pomalyst, Farydak, Ninlaro and Kyprolis for additional safety information for the combination regimens in multiple myeloma.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 3. HEMADY Regulatory History

Date	Event Type	Purpose
January 14, 2016	Pre-IND Meeting	Discussion of bioequivalence study to support a scientific bridge to Decadron
November 8, 2017	Pre-NDA meeting	To discuss the content of the NDA
March 22, 2018	Amended iPSP Agreed upon	
March 26, 2018	Orphan Designation Granted	

Source: FDA Clinical Reviewer

The Applicant initially submitted NDA 21137 on September 6, 2018 for the following proposed indications:

(b) (4)

This application was discussed with the Medical Policy Council (MPC) and the Oncology Center of Excellence (OCE). The Agency determined that, based on the widespread use of dexamethasone in combination with other anti-myeloma products, a broad indication for dexamethasone in multiple myeloma would be appropriate at this time. The Applicant subsequently submitted a Major Amendment to the application on June 21, 2019.

2.6 Other Relevant Background Information

To support this 505(b)(2) application, the Applicant is relying on the previous findings of safety and efficacy data from the labels of the listed drugs, as well as from published literature describing clinical studies conducted with dexamethasone in combination with these drugs.

This application is relying on results from a total of 20 clinical studies. Of these, five were conducted in patients with newly diagnosed multiple myeloma, and 15 were conducted in patients with relapsed or refractory multiple myeloma. Of the 20 studies, 14 are reported in the prescribing information for the following listed drugs: Thalomid,

Velcade, Revlimid, Pomalyst, Farydak, Ninlaro and Kyprolis. Six additional studies are reported in the literature.

An overview of the studies the application relies on, as well as the supportive studies, are provided in the Tables below.

Table 4: Listing of Studies Relied Upon

Source of Information Author, year	Study design Phase, Location	Dexamethasone / Combination treatment (drug/dexamethasone)	n (per treatment group)	n (total)	Information Provided	Rely/ Support
Studies being relied on to support dexamethasone in combination with thalidomide for the treatment of newly diagnosed patients with MM						
Rajkumar et al., (2006); Thalomid PI (2017)	Phase 3 Randomized, open label multi-center, U.S. (ECOGE1A00)	Thalidomide + dexamethasone	n = 103	n = 207	Efficacy of dexamethasone in combination with thalidomide for the treatment of newly diagnosed MM patients	Rely
		Dexamethasone	n = 104			
Rajkumar et al., (2008); Thalomid PI (2017)	Phase 3 Randomized, double-blind, placebo-controlled, 99 centers (U.S., Europe, Australia, Asia)	Thalidomide + dexamethasone	n = 235	n = 470	Efficacy of dexamethasone in combination with thalidomide for the treatment of newly diagnosed MM patients	Rely
		Dexamethasone	n = 235			
Studies being relied on to support dexamethasone in combination with lenalidomide for the treatment of newly diagnosed patients with MM						
Revlimid PI (2019); Benboubker et al. (2014)	Phase 3 - NCT00689936 Randomized, Open-label Multicenter: 246 centers (Europe, North America, Asia-Pacific region)	Lenalidomide + dexamethasone (Continuous)	n = 535	n = 1623	Efficacy and safety of low-dose dexamethasone in combination with lenalidomide for the treatment of newly diagnosed MM patients.	Rely
		Lenalidomide + dexamethasone (Rd 18 up to 18 28-day cycle)	n = 541			
		Melphalan + prednisone + thalidomide (MPT)	n = 547			

Studies being relied on to support dexamethasone in combination with bortezomib and lenalidomide (VRd) for the treatment of newly diagnosed patients with MM						
Source of Information Author, year	**Study design Phase, Location**	**Dexamethasone / Combination treatment (drug/dexamethasone)**	**n (per treatment group)**	**n (total)**	**Information Provided**	**Rely/ Support**
Durie et al. (2017)	Phase 3 - NCT00644228 Open-label, Multicenter (US)	Bortezomib + Lenalidomide + Dexamethasone (VRd)	n = 264	n = 525	Efficacy and safety of bortezomib in combination with lenalidomide and dexamethasone (VRd) versus lenalidomide-dexamethasone (Rd) as induction treatment in patients with newly diagnosed MM.	Rely
		Lenalidomide + Dexamethasone (Rd)	n = 261			
Attal et al. (2017)	Phase 3 - NCT01191060 Randomized, Open-label Multicenter (Europe)	Bortezomib + Lenalidomide + Dexamethasone (3 cycles of VRd) + consolidation therapy (5 additional cycles of VRd)	n = 350	n = 700	Efficacy and safety of the drug combination VRd alone versus VRd with high-dose chemotherapy plus autologous stem-cell transplantation in patients with newly diagnosed MM.	Rely
		Bortezomib + Lenalidomide + Dexamethasone (3 cycles of VRd) + consolidation therapy (high-dose melphalan + stem-cell transplantation + 2 additional cycles of VRd)	n = 350			
Studies being relied on to support dexamethasone in combination with bortezomib for the treatment of relapsed MM						
Richardson et al., (2003); Jagannath et al., (2006)	Phase 2 Open label, non- randomized 14 centers, U.S.	Bortezomib-dexamethasone	n = 78	n = 202	Efficacy of dexamethasone in combination with bortezomib for the treatment of relapsed, refractory MM	Rely
		Bortezomib	n=124			
Jagannath et al., (2004); Jagannath et al., (2006)	Phase 2 Open label, randomized 10 Centers, U.S.	Bortezomib-dexamethasone	n = 28	n = 54	Efficacy of dexamethasone in combination with bortezomib for the treatment of relapsed or refractory MM	Rely
		Bortezomib	n=26			
Source of Information Author, year	**Study design Phase, Location**	**Dexamethasone / Combination treatment (drug/dexamethasone)**	**n (per treatment group)**	**n (total)**	**Information Provided**	**Rely/ Support**
Petrucci et al., (2013); Velcade PI (2019)	Phase 2 55 centers in Austria, Belgium, France, Germany, Greece, Italy, Luxembourg, Portugal and Spain.	Bortezomib-dexamethasone	n = 94	n = 130	Efficacy of dexamethasone in combination with bortezomib for the treatment of relapsed MM	Rely
		Bortezomib	n=36			
Mikhael et al., (2009)	Phase 3 Open label 93 centers in North/South America, Australia, Europe, and Asia	Bortezomib-dexamethasone	n = 208	n = 608	Efficacy of dexamethasone in combination with bortezomib for the treatment of relapsed or refractory MM	Rely
		Bortezomib	n=430			
Moreau et al., (2011b); Velcade PI (2019); Arnulf et al., (2012)	Phase 3 - NCT00722566 Randomized, open label 53 centers in Europe, Asia, and South America	Bortezomib + dexamethasone	n = 121	n = 222	Efficacy of dexamethasone in combination with bortezomib for the treatment of relapsed MM	Rely
		Bortezomib	n = 101			
Dimopoulos et al., (2015)	Retrospective, matched-pairs analysis of Phase 2 (MMY-2045), and Phase 3 (MMY-3001, APEX) Studies were multicenter across North and South America, Asia, Africa, Europe and Australia	Bortezomib + dexamethasone	n = 109	n = 218	Efficacy of dexamethasone in combination with bortezomib for the treatment of relapsed MM	Rely
		Bortezomib	n = 109			

Source of Information Author, year	Study design Phase, Location	Dexamethasone / Combination treatment (drug/dexamethasone)		n (per treatment group)	n (total)	Information Provided	Rely/ Support
Studies being relied on to support dexamethasone in combination with lenalidomide for the treatment of patients who had received at least one prior therapy							
Revlimid PI (2019); Weber et al. (2007); Dimopoulos et al. (2007)	Two Phase 3 (NCT00056160 and NCT00424047) double-blind, placebo controlled studies NCT00056160 multicenter study (44 centers in US and Canada) NCT00424047 multicenter (41 centers in Europe, 6 centers in Australia, and 3 centers in Israel)	Study 1	Lenalidomide + dexamethasone	n = 177	n = 353	Efficacy and safety of dexamethasone in combination with lenalidomide for the treatment of patients who had received at least one prior therapy	Rely
			Placebo + dexamethasone	n = 176			
		Study 2	Lenalidomide + dexamethasone	n = 176	n = 351		
			Placebo + dexamethasone	n = 175			
Studies being relied on to support dexamethasone in combination with pomalidomide for the treatment of refractory/relapsed MM							
Pomalyst PI (2018); Richardson et al. (2014)	NCT00833833 -Phase 2, Randomized, Open-label Multicenter: 19 centers in US and Canada	Pomalidomide		n = 108	n = 221	Efficacy and safety of dexamethasone in combination with pomalidomide in patients with relapsed MM who were refractory to their last myeloma therapy and had received lenalidomide and bortezomib	Rely
		Pomalidomide + dexamethasone		n = 113			

Source of Information Author, year	Study design Phase, Location	Dexamethasone / Combination treatment (drug/dexamethasone)	n (per treatment group)	n (total)	Information Provided	Rely/ Support
Pomalyst PI (2018); San Miguel et al. (2013)	NCT01311687 - Phase 3 Randomized, Open-label Multicenter: 93 sites in Europe, Australia, Canada, Russia, US	Pomalidomide + low-dose dexamethasone	n = 302	n = 455	Efficacy and safety of dexamethasone in combination with pomalidomide compared to high-dose dexamethasone in patients with relapsed and refractory MM, who had received at least two prior treatment regimens, including lenalidomide and bortezomib, and demonstrated disease progression on or within 60 days of the last therapy	Rely
		High-dose dexamethasone	n = 153			
Studies being relied on to support dexamethasone in combination with panobinostat for the treatment of refractory/relapsed MM						
Farydak PI (2015); San Miguel et al. (2014); Richardson et al. (2016); San Miguel et al. (2016)	NCT01023308 Phase 3, randomized, double-blind, placebo-controlled Multicenter: 215 centers across 34 countries (North and Central America, Europe, Asia-Pacific region, Middle East, South America, Africa)	Panobinostat + bortezomib + dexamethasone	n = 387	n = 768	Efficacy and safety of dexamethasone in combination with panobinostat and bortezomib in patients with relapsed MM. who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent.	Rely
		Placebo + Bortezomib + dexamethasone	n = 381			

Studies being relied on to support dexamethasone in combination with ixazomib for the treatment of refractory/relapsed MM						
Source of Information Author, year	**Study design Phase, Location**	**Dexamethasone / Combination treatment (drug/dexamethasone)**	**n (per treatment group)**	**n (total)**	**Information Provided**	**Rely/ Support**
Ninlaro PI (2016); Moreau et al. (2016b); Mateos et al. (2017); Avet-Loiseau et al. (2017)	NCT01564537- Phase 3 TOURMALINE-MM1 Randomized, double-blind, placebo-controlled Multicenter : 147 sites in 26 countries (Australia, Europe, North America, Asia-Pacific region, Middle East)	Ixazomib + Lenalidomide + dexamethasone	n = 360	n = 722	Efficacy and safety of dexamethasone in combination with ixazomib and lenalidomide in patients with relapsed and/or refractory MM who have received at least one prior therapy	Rely
		Placebo + Lenalidomide + dexamethasone	n = 362			
Studies being relied on to support dexamethasone in combination with carfilzomib for the treatment of refractory/relapsed MM						
Kyprolis PI (2019); Stewart et al. (2015); Avet-Loiseau et al. (2016); Dimopoulos et al. (2017a); Dimopoulos et al. (2017b); Siegel et al. (2018)	NCT01080391 - ASPIRE Phase 3, randomized, open-label Multicenter: 127 sites in Europe, North America, the Middle East	Carfilzomib + Lenalidomide + dexamethasone	n = 396	n = 792	Efficacy and safety of dexamethasone in combination with carfilzomib and lenalidomide in patients with relapsed MM patients with relapsed or refractory MM who have received one to three lines of therapy.	Rely
		Lenalidomide + dexamethasone	n = 396			
Kyprolis PI (2019); Dimopoulos et al. (2016); Dimopoulos et al. (2017); Moreau et al. (2017); Chng et al. (2017); Ludwig et al. (2019)	NCT01568866 - Phase 3 ENDEAVOR Randomized, Open-label Multicenter: 198 centers in 27 countries in Europe, North America, South America, and the Asia-Pacific region.	Carfilzomib + dexamethasone	n = 464	n = 929	Efficacy and safety of dexamethasone in combination with carfilzomib in patients with relapsed MM patients with relapsed or refractory MM who have received one to three lines of therapy	Rely
		Bortezomib + dexamethasone	n = 465			
Kyprolis PI (2019); Moreau et al. (2018)	NCT02412878- A.R.R.O.W. Phase 3, randomized, open-label study Multicenter: 118 sites in Asia-Pacific region, North America, and Europe.	Carfilzomib + dexamethasone (once weekly)	n = 240	n = 478	Efficacy and safety of dexamethasone in combination with carfilzomib administered once weekly or twice weekly for the treatment of relapsed MM patients with relapsed or refractory MM who had received one to three lines of therapy.	Rely
		Carfilzomib + dexamethasone (twice weekly)	n = 238			

Source: Applicant's Summary of Clinical Efficacy

Table 5: Supportive Studies

Montefusco et al., (2013)	Phase 2 – (EudraCT number: 2006-004815-24) Four hematology centers in Italy	Bortezomib + dexamethasone	n = 19	n = 19	Efficacy and safety of dexamethasone in combination with bortezomib for the treatment of relapsed/refractory MM patients	Support
Harrison et al., (2015)	Phase 2 - NCT00335348 Open label Multi-center study (20 centers in Australia and New Zealand)	Bortezomib + dexamethasone	n = 100	n = 100	Efficacy and safety of dexamethasone in combination with bortezomib for the treatment of relapsed/refractory MM patients	Support
Source of Information Author, year	**Study design Phase, Location**	**Dexamethasone / Combination treatment (drug/dexamethasone)**	**n (per treatment group)**	**n (total)**	**Information Provided**	**Rely/ Support**
Ozaki et al., (2016)	Phase 2 (UMIN-000003345) Multi-center study (16 centers in Japan)	Bortezomib + dexamethasone	n = 47	n = 47	Efficacy and safety of dexamethasone in combination with bortezomib for the treatment of relapsed/refractory MM elderly patients	Support
Cavo et al., (2012); Cavo et al., (2010)	Phase 3- NCT01134484randomized, open label 73 hospitals in Italy	Thalidomide + dexamethasone	n = 239	n = 480	Efficacy of dexamethasone in combination with thalidomide as an induction therapy before, and after consolidation therapy, after double autologous cell transplantation for the treatment of newly diagnosed MM patients	Support
		Thalidomide + dexamethasone + bortezomib	n = 241			
Rosinol et al., (2012)	Phase 3 - NCT00461747 Randomized, controlled 66 centers in Spain	Bortezomib + thalidomide + dexamethasone	n = 130	n = 386	Efficacy of dexamethasone in combination with thalidomide as induction therapy in newly diagnosed MM patients	Support
		Thalidomide + dexamethasone	n = 127			
		Vincristine + bis-chloroethylnitrosourea (BCNU) + melphalan + cyclophosphamide + prednisone/vincristine + BCNU + doxorubicin + dexamethasone + bortezomib	n = 129			
Hjorth et al., (2012)	Phase 3 - NCT00602511 Randomized, open label 29 hospitals in Sweden, Denmark, and Norway	Bortezomib + dexamethasone	n = 64	n = 131	Efficacy of dexamethasone in combination with bortezomib for the treatment of relapsed MM	Support
		Thalidomide + dexamethasone	n = 67			

Source of Information Author, year	Study design Phase, Location	Dexamethasone / Combination treatment (drug/dexamethasone)	n (per treatment group)	n (total)	Information Provided	Rely/ Support
Kropff et al., (2017)	Phase 3 – NCT00813150 Open label, randomized, controlled 42 centers in Germany	Bortezomib + dexamethasone	n = 48	n = 96	Efficacy of dexamethasone in combination with bortezomib for the treatment of primary refractory or relapsed MM	Support
		Bortezomib + dexamethasone + cyclophosphamide	n = 48			
Richardson et al. (2010)	Phase 1/2 - NCT00378105 open-label study Multicenter study (6 centers in the US)	Bortezomib + lenalidomide + dexamethasone	n = 31 (phase 1) n = 35 (phase 2)	n = 66	Efficacy and safety of bortezomib in combination with lenalidomide and dexamethasone in patients with newly diagnosed MM.	Support
Kumar et al. (2012)	Phase 1/2 - NCT00507442 EVOLUTION study Randomized, Open-label Multicenter: 24 centers (US)	Bortezomib + Lenalidomide + Dexamethasone (VRD)	n = 42	n = 140	Efficacy and safety of treatment combinations VDCR, VRD, VDC, and VDC-mod in patients with previously untreated MM.	Support
		Bortezomib + Lenalidomide + Dexamethasone + Cyclophosphamide (VDCR)	n = 66			
		Bortezomib + Dexamethasone + Cyclophosphamide (VDC)	n = 33			
		Bortezomib modified dosing + Dexamethasone + Cyclophosphamide (VDC mod)	n = 17			
Roussel et al. (2014)	Phase 2 - NCT01206205 single-arm, open-label Multicenter study (France)	Bortezomib + Lenalidomide + dexamethasone (3 induction cycles) + cyclophosphamide harvest and transplantation + RVD consolidation (2 cycles) + 1-year lenalidomide maintenance	n = 31	n = 31	Evaluate VRd induction and consolidation therapies in a sequential intensive strategy for previously untreated transplantation-eligible patients with MM.	Support
Chakraborty et al.(2017)	Retrospective analysis	Cyclophosphamide-lenalidomide-dexamethasone (CyBorD)	n = 193	n = 1017	The study demonstrated that among patients completing induction therapy and continuing to early transplant, VRd induction leads to improved overall survival compared to CyBorD and Vd regimens.	Support
		Bortezomib-dexamethasone (Vd)	n = 64			
		Lenalidomide-dexamethasone (Rd)	n = 251			
		Bortezomib-lenalidomide-dexamethasone (VRd)	n = 126			
		Thalidomide-dexamethasone	n = 155			
		Vincristine-doxorubicin-dexamethasone or dexamethasone alone (VAD/Dex)	n = 228			
O'Donnell et al. (2018)	Phase 2 - NCT01782963 single-arm Multicenter (US)	Bortezomib + Lenalidomide + dexamethasone (VRd lite)	n = 50	n = 50	Efficacy of modified lenalidomide, bortezomib and dexamethasone for Transplant-Ineligible Patients With Newly Diagnosed Multiple Myeloma.	Support

Source: Applicant's Summary of Clinical Efficacy

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was provided in accordance with the International Conference on Harmonization Electronic Common Technical Document (eCTD).

3.2 Compliance with Good Clinical Practices

Not applicable.

3.3 Financial Disclosures

The applicant submitted financial disclosure information for investigators for the bioequivalence study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Refer to the CMC Review.

4.2 Clinical Microbiology

Refer to the CMC Review.

4.3 Preclinical Pharmacology/Toxicology

Refer to the Pharmacology-Toxicology Review.

4.4 Clinical Pharmacology

Refer to the Clinical Pharmacology Review.

5 Sources of Clinical Data

No clinical data was included in this application.

6 Review of Efficacy

Efficacy Summary

The Applicant did not conduct any clinical efficacy studies in support of this application. The scientific bridge to West-Ward's dexamethasone 4 mg tablet (ANDA 084612) was established using a pharmacokinetic (PK) study conducted by the Applicant (see Clinical Pharmacology review for additional details). In order to support the proposed indication, the Applicant is relying on the FDA's findings of efficacy for Thalomid, Velcade, Revlimid, Pomalyst, Ninlaro, Farydak and Kyprolis, as well as the published literature describing the results of clinical studies using dexamethasone in combination with these anti-myeloma drugs. Refer to the approved labeling for these anti-myeloma drugs for additional information.

7 Review of Safety

Safety Summary

The safety of dexamethasone is supported by the following:

- The listed drug Decadron (NDA 011664).
- The PK study conducted for this application (Study 160458)
- Twenty Phase 2 and 3 studies that support the safety of dexamethasone in combination with anti-myeloma drugs. Of these, 14 are reported in the prescribing information for the following listed drugs: Thalomid, Velcade, Revlimid, Pomalyst, Farydak, Ninlaro and Kyprolis. Six additional studies are reported in the literature.
- Additional literature identified in the public domain that describes studies which evaluated combination regimens of dexamethasone with anti-myeloma drugs or dexamethasone as monotherapy in patients with multiple myeloma.

A total of 8006 patients with multiple myeloma have reported adverse events associated with dexamethasone in the FAERs database between 2010-2018. The patterns of adverse events reported were similar to the events reported in the clinical studies that are included in the Prescribing Information for Decadron. Most of these events were associated with dexamethasone and additional anti-myeloma drugs and are included in the labeling for these products. Collectively, the overall safety narrative and the post-marketing safety database data are similar to that described in the labeling of the listed drugs.

9 Appendices

9.1 Literature Review/References

1. Decadron®. Prescribing Information. 2019.
2. Thalomid®. Prescribing Information. Celgene Corporation. 2017.
3. Revlimid®. Prescribing Information. Celgene Corporation. 2019.
4. Velcade®. Prescribing Information. Millennium Pharmaceuticals, Inc. 2019.
5. Pomalyst®. Prescribing Information. Celgene Corporation. 2018.
6. Farydak®. Prescribing Information. Novartis Corporation. 2015.
7. Ninlaro®. Prescribing Information. Millennium Pharmaceuticals, Inc. 2016.
8. Kyprolis®. Prescribing Information. Onyx Pharmaceuticals, Inc. 2019.
9. Alexanian, R., Barlogie, B., Dixon, D. High-dose glucocorticoid treatment of resistant myeloma. *Annals of Internal Medicine*. 1986;105(1):8-11.
10. Alexanian, R., Dimopoulos, M.A., Delasalle, K., Barlogie, B. Primary dexamethasone treatment of multiple myeloma. *Blood.* 1992;80(4):887-890.
11. Kumar, S.K., Callander, N.S., Alsina, M. Atanackovic, D., Biermann, J.S., Castillo, J., Chandler, J.C., Costello, C., Faiman, M., Fung, H.C., Godby, K. NCCN guidelines insights: multiple myeloma version 3. *Journal of the National Comprehensive Cancer Network.* 2018;16(1):11-20.
12. Sharma, S, Lichtenstein, A. Dexamethasone-induced apoptotic mechanisms in myeloma cells investigated by analysis of mutant glucocorticoid receptors. *Blood.* 2008;112(4):1338-1345.

9.2 Labeling Recommendations

Labeling negotiations are ongoing. HEMADY will not be indicated for the indications listed in the Decadron labeling. Labeling will be based on the Decadron labeling that is applicable for this indicated patient population.

9.3 Advisory Committee Meeting

This application was not taken to an Oncologic Drugs Advisory Committee.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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