Only for the use of a Registered Medical Practitioner or a Hospital or a Laboratory.

Biocon

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Lenalidomide Capsules

HUMIX® 5/10/25

WrÉEqÉYxÉ 5/10/25

Compostion:

HUMIX® 5
Each capsule contains
Lenalidomide 5 mg

HUMIX® 10
Each capsule contains
Lenalidomide 10 mg

HUMIX® 25
Each capsule contains
Lenalidomide 25 mg

Warnings:
Potential for human birth defects - Lenalidomide is an analogue of thalidomide. Thalidomide is a known human teratogen that causes life-threatening human birth defects. The teratogenic effect of Lenalidomide in humans cannot be ruled out. Lenalidomide may cause fetal harm when administered to a pregnant female. Females of childbearing potential should be advised to avoid pregnancy while on Lenalidomide.

Hematologic toxicity (Neutropenia and Thrombocytopenia)- Lenalidomide is associated with significant neutropenia and thrombocytopenia.

Deep venous thrombosis (DVT) and pulmonary embolism (PE)- Lenalidomide has demonstrated a significantly increased risk of DVT and PE in patients with multiple myeloma who were treated with Lenalidomide combination therapy. Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling.

DESCRIPTION
Lenalidomide, a thalidomide analogue, is an immunomodulatory agent with antiangiogenic and antineoplastic properties. The chemical name is 3-(4-amino-1-oxo 1, 3-dihydro-2H-isoindol-2-yl) piperidine-2, 6-dione, with its empirical formula is $C_{13}H_{13}N_3O_3$ and the gram molecular weight is 259.3. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

CLINICAL PHARMACOLOGY
Mechanism of action
The mechanism of action of Lenalidomide remains to be fully characterized. Lenalidomide possesses immunomodulatory, antiangiogenic, and antineoplastic properties. Experiments have demonstrated that Lenalidomide inhibits the growth of cells derived from patients with multiple myeloma and del (5q) myelodysplastic syndromes in vitro. Lenalidomide causes a delay in tumor growth in some in vivo nonclinical hematopoietic tumor models, including multiple myeloma. Lenalidomide inhibits the secretion of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), from peripheral blood mononuclear cells. Lenalidomide also inhibited the expression of cycoloxygenase-2 (COX-2) but not COX-1 in vitro.

Pharmacokinetics
Absorption – Lenalidomide in healthy volunteers is rapidly absorbed following oral absorption with maximum plasma concentration occurring between 0.625 and 1.5 hours post dose. Co-administration with food does not alter the extent of absorption (AUC) but reduces the maximal plasma concentration Cmax by 36%. The pharmacokinetic disposition of Lenalidomide is linear. Cmax and AUC increase proportionately with increases in dose. Multiple dosing at the recommended dose regimen does not result in drug accumulation. Exposure (AUC) in multiple myeloma (MM) patients was observed to be 57 % than healthy male volunteers.
Distribution – In vitro (14C)-Lenalidomide binding to plasma proteins is approximately 30%.
Metabolism and Excretion – The metabolic profile of Lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of Lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half-life of elimination is approximately 3 hours.

INDICATIONS AND USAGE
Multiple Myeloma
HUMIX® in combination with dexamethasone is indicated for the treatment of patients with multiple myeloma (MM) who have received at least one prior therapy.

Myelodysplastic Syndromes
HUMIX® is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

Clinical Studies
Multiple Myeloma - Two randomized studies (Studies 1 and 2) were conducted to evaluate the efficacy and safety of Lenalidomide. These multicenter, multinational, double-blind, placebo-controlled studies compared Lenalidomide plus oral pulse high-dose dexamethasone therapy to dexamethasone therapy alone in patients with multiple myeloma who had received at least one prior treatment. These studies enrolled patients with absolute neutrophil counts (ANC) ≥1000/mm³, platelet counts ≥75,000/mm³, serum creatinine ≤2.5mg/dL, serum SGOT/AST or SGPT/ALT ≤3.0 x upper limit of normal (ULN), and serum direct bilirubin ≤2.0 mg/dL. In both studies, patients in the Lenalidomide /Dexamethasone group took 25 mg of Lenalidomide orally once daily on Days 1 to 21 and a matching placebo capsule once daily on Days 22 to 28 of each 28-day cycle. Patients in the placebo/dexamethasone group took 1 placebo capsule on Days 1 to 28 of each 28-day cycle. Patients in both treatment groups took 40 mg of dexamethasone orally once daily on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy. The dose of Dexamethasone was reduced to 40 mg orally once daily on Days 1 to 4 of each 28-day cycle after the first 4 cycles of therapy. In both studies, treatment was to continue until disease progression. In both studies, dose adjustments were allowed based on clinical and laboratory findings. Sequential dose reductions to 15 mg daily, 10 mg daily and 5 mg daily were allowed for toxicity.

Table 1 summarizes the baseline patient and disease characteristics in the two studies. In both studies, baseline demographic and disease-related characteristics were comparable between the Lenalidomide /Dexamethasone and placebo/Dexamethasone groups.

Table 1: Baseline Demographic and Disease-Related Characteristics – Studies 1 and 2

	Study 1		Study 2	
	Lenalidomide/Dex N=177	Placebo/Dex N=176	Lenalidomide /Dex N=176	Placebo/Dex N=175
Patient Characteristics				
Age (years)				
Median	64	62	63	64
Min, Max	36, 86	37, 85	33, 84	40, 82
Sex				
Male	106 (60%)	104 (59%)	104 (59%)	103 (59%)
Female	71 (40%)	72 (41%)	72 (41%)	72 (41%)
Race/Ethnicity				
White	141(80%)	148 (84%)	172 (98%)	175(100%)
Other	36 (20%)	28 (16%)	4 (2%)	0 (0%)
ECOG Performance				
Status 0-1	157 (89%)	168 (95%)	150 (85%)	144 (82%)
Disease Characteristics				
Multiple Myeloma Stage (Durie-Salmon)				
I	3%	3%	6%	5%
II	32%	31%	28%	33%
III	64%	66%	65%	63%
B2-microglobulin (mg/L)				
≥2.5 mg/L	52 (29%)	51 (29%)	51 (29%)	48 (27%)
> 2.5 mg/L	125 (71%)	125 (71%)	125 (71%)	127 (73%)
Number of Prior Therapies				
1	38%	38%	32%	33%
≥ 2	62%	62%	68%	67%
Types of Prior Therapies				
Stem Cell Transplantation	62%	61%	55%	54%
Thalidomide	42%	46%	30%	38%
Dexamethasone	81%	71%	66%	69%
Bortezomib	11%	11%	5%	4%
Melphalan	33%	31%	56%	52%
Doxorubicin	55%	51%	56%	57%

The primary efficacy endpoint in both studies was time to progression (TTP). TTP was defined as the time from randomization to the first occurrence of progressive disease.

Preplanned interim analyses of both studies showed that the combination of Lenalidomide/Dexamethasone was significantly superior to Dexamethasone alone for TTP. The studies were unblinded to allow patients in the placebo/Dexamethasone group to receive treatment with the Lenalidomide /Dexamethasone combination. For both studies, the extended follow-up survival data with crossovers were analyzed. In study 1, the median survival time was 39.4 months (95%CI: 32.9, 47.4) in Lenalidomide /Dexamethasone group and 31.6 months (95%CI: 24.1, 40.9) in placebo/dexamethasone group, with a hazard ratio of 0.79 (95% CI: 0.61-1.03). In study 2, the median survival time was 37.5 months (95%CI: 29.9, 46.6) in Lenalidomide /Dexamethasone group and 30.8 months (95%CI: 23.5, 40.3) in placebo/Dexamethasone group, with a hazard ratio of 0.86 (95% CI: 0.65-1.14).

Table 2: TTP Results in Study 1 and Study 2

	Study 1		Study 2	
	Lenalidomide/Dex N=177	Placebo/Dex N=176	Lenalidomide /Dex N=176	Placebo/Dex N=175
TTP				
Events n (%)	73 (41)	120 (68)	68 (39)	130 (74)
Median TTP in months [95% CI]	13.9 [9.5, 18.5]	4.7 [3.7, 4.9]	12.1 [9.5, NE]	4.7 [3.8, 4.8]
Hazard Ratio [95% CI]	0.285 [0.210,0.386]		0.324 [0.240,0.438]	
Log-rank Test p-value 3	< 0.001		< 0.001	
Response				
Complete Response (CR) n (%)	23 (13)	1 (1)	27 (15)	7 (4)
Partial Response (RR/PR) n (%)	84 (48)	33 (19)	77 (44)	34 (19)
Overall Response n (%)	107 (61)	34 (19)	104 (59)	41 (23)
p-value	< 0.001		< 0.001	
Odds Ratio [95% CI]	6.38 [3.95,10.32]		4.72 [2.98,7.49]	

Myelodysplastic Syndromes (MDS) with a Deletion 5q Cytogenetic Abnormality - The efficacy and safety of Lenalidomide were evaluated in patients with transfusion-dependent anemia in low- or intermediate-1- risk MDS with a 5q (q31-33) cytogenetic abnormality in isolation or with additional cytogenetic abnormalities, at a dose of 10 mg once daily or 10 mg once daily for 21 days every 28 days in an open-label, single-arm, multi-center study. The major study was not designed nor powered to prospectively compare the efficacy of the 2 dosing regimens. Sequential dose reductions to 5 mg daily and 5 mg every other day, as well as dose delays, were allowed for toxicity.

This major study enrolled 148 patients who had RBC transfusion dependent anemia. RBC transfusion dependence was defined as having received ≥2units of RBCs within 8 weeks prior to study treatment. The study enrolled patients with absolute neutrophil counts (ANC) ≥500/mm³, platelet counts ≥50,000/ mm³, serum creatinine ≤2.5mg/dL, serum SGOT/AST or SGPT/ALT ≤3.0 x upper limit of normal (ULN), and serum direct bilirubin ≤2.0 mg/dL. Granulocyte colony-stimulating factor was permitted for patients who developed neutropenia or fever in association with neutropenia. Baseline patient and disease-related characteristics are summarized in Table 3.

Table 3: Baseline Demographic and Disease-Related Characteristics in the MDS Study

	Overall (N=148)	
Age (years)		
Median	71.0	
Min, Max	37.0,95.0	
Gender	**n**	**(%)**
Male	51	(34.5)
Female	97	(65.5)
Race	**n**	**(%)**
White	143	(96.6)
Other	5	(3.4)
Duration of MDS (years)		
Median	2.5	
Min, Max	0.1,20.7	
Del 5 (q31-33) Cytogenetic Abnormality	**n**	**(%)**
Yes	148	(100.0)
Other cytogenetic abnormalities	37	(25.2)
IPSS Score [a]	**n**	**(%)**
Low (0)	55	(37.2)
Intermediate-1 (0.5-1.0)	65	(43.9)
Intermediate-2 (1.5-2.0)	6	(4.1)
High (⩾ 2.5)	2	(1.4)
Missing	20	(13.5)
FAB Classification [b]from central review	**n**	**(%)**
RA	77	(52.0)
RARS	16	(10.8)
RAEB	30	(20.3)
CMML	3	(2.0)

[a] IPSS Risk Category: Low (combined score = 0), Intermediate-1 (combined score = 0.5 to 1.0), Intermediate-2 (combined score = 1.5 to 2.0), High (combined score ⩾ 2.5):Combined score= (Marrow blast score + Karyotype score + Cytopenia score)
[b] French-American-British (FAB) classification of MDS.

The frequency of RBC transfusion independence was assessed using criteria modified from the International Working Group (IWG) response criteria for MDS. RBC transfusion independence was defined as the absence of any RBC transfusion during any consecutive "rolling" 56 days (8 weeks) during the treatment period.

Transfusion independence was seen in 99/148 (67%) patients (95% CI [59, 74]). The median duration from the date when RBC transfusion independence was first declared (i.e., the last day of the 56-day RBC transfusion-free period) to the date when an additional transfusion was received after the 56-day transfusion-free period among the 99 responders was 44 weeks (range of 0 to > 67 weeks).

Ninety percent of patients who achieved a transfusion benefit did so by completion of three months in the study.

RBC transfusion independence rates were unaffected by age or gender. The dose of Lenalidomide was reduced or interrupted at least once due to an adverse event in 118 (79.7%) of the 148 patients; the median time to the first dose reduction or interruption was 21 days (mean, 35.1 days; range, 2-253 days), and the median duration of the first dose interruption was 22 days (mean, 28.5 days; range, 2-265 days). A second dose reduction or interruption due to adverse events was required in 50 (33.8%) of the 148 patients. The median interval between the first and second dose reduction or interruption was 51 days (mean, 59.7 days; range, 15-205 days) and the median duration of the second dose interruption was 21 days (mean, 26 days; range, 2-148 days).

CONTRAINDICATIONS
Pregnancy – Lenalidomide may cause fetal harm when administered to a pregnant woman. Limb abnormalities were seen in the offspring of monkeys that were dosed with Lenalidomide during organogenesis. Females of childbearing potential may be treated with Lenalidomide provided adequate precautions are taken to avoid pregnancy.
Allergic reactions – Lenalidomide is contraindicated in patients who have demonstrated hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to Lenalidomide.

WARNINGS AND PRECAUTIONS
Pregnancy Category X - Lenalidomide is an analogue of thalidomide. Thalidomide is a known human teratogen that causes life-threatening human birth defects.

Hematologic toxicity (Neutropenia and Thrombocytopenia) - Lenalidomide is associated with significant neutropenia and thrombocytopenia. Patients taking Lenalidomide should have their complete blood counts monitored.

Deep venous thrombosis (DVT) and pulmonary embolism (PE) - Lenalidomide has demonstrated a significantly increased risk of DVT and PE in patients with multiple myeloma who were treated with Lenalidomide combination therapy. Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling.

Allergic Reactions - Angioedema and serious dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. These events can be fatal.
Tumor Lysis Syndrome - Fatal instances of tumor lysis syndrome have been reported during treatment with Lenalidomide.
Tumor Flare Reaction - Tumor flare reaction has occurred during investigational use of Lenalidomide for CLL and lymphoma, and is characterized by tender lymph node swelling, low grade fever, pain and rash.

SIDE EFFECTS
Clinical Trials Experience in Multiple Myeloma
Data were evaluated from 703 patients in two studies who received at least one dose of Lenalidomide/Dexamethasone (353 patients) or placebo/Dexamethasone (350 patients).

Tables 4, 5, and 6 summarize the adverse reactions reported for Lenalidomide/Dexamethasone and placebo/Dexamethasone groups.

Table 4: Adverse Reactions Reported in ≥5% of Patients and with a ≥ 2% Difference in Proportion of Patients Between the Lenalidomide/ Dexamethasone and Placebo/Dexamethasone Groups

System Organ Class/ Preferred Term	Lenalidomide/Dex* (n=353) n (%)	Placebo/Dex * (n=350) n (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Neutropenia [%]	149 (42.2)	22 (6.3)
Anemia [@]	111 (31.4)	83 (23.7)
Thrombocytopenia [@]	76 (21.5)	37 (10.6)
Leukopenia	28 (7.9)	4 (1.1)
Lymphopenia	19 (5.4)	5 (1.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue	155 (43.9)	146 (41.7)
Pyrexia	97 (27.5)	82 (23.4)
Peripheral edema	93 (26.3)	74 (21.1)
Chest Pain	29 (8.2)	20 (5.7)
Lethargy	24 (6.8)	8 (2.3)
GASTROINTESTINAL DISORDERS		
Constipation	143 (40.5)	74 (21.1)
Diarrhea[@]	136 (38.5)	96 (27.4)
Nausea [@]	92 (26.1)	75 (21.4)
Vomiting [@]	43 (12.2)	33 (9.4)
Abdominal Pain [@]	35 (9.9)	22 (6.3)
Dry Mouth	25 (7.1)	13 (3.7)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Muscle cramp	118 (33.4)	74 (21.1)
Back pain	91 (25.8)	65 (18.6)
Bone Pain	48 (13.6)	39 (11.1)
Pain in Limb	42 (11.9)	32 (9.1)
NERVOUS SYSTEM DISORDERS		
Dizziness	82 (23.2)	59 (16.9)
Tremor	75 (21.2)	26 (7.4)
Dysgeusia	54 (15.3)	34 (9.7)
Hypoaesthesia	36 (10.2)	25 (7.1)
Neuropathy [^]	23 (6.5)	13 (3.7)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Dyspnea	83 (23.5)	60 (17.1)
Nasopharyngitis	62 (17.6)	31 (8.9)
Pharyngitis	48 (13.6)	33 (9.4)
Bronchitis	40 (11.3)	30 (8.6)
INFECTIONS[$] AND INFESTATIONS		
Upper respiratory tract infection	87 (24.6)	55 (15.7)
Pneumonia [@]	48 (13.6)	29 (8.3)
Urinary Tract Infection	30 (8.5)	19 (5.4)
Sinusitis	26 (7.4)	16 (4.6)
SKIN AND SUBCUTANEOUS SYSTEM DISORDERS		
Rash [£]	75 (21.2)	33 (9.4)
Sweating Increased	35 (9.9)	25 (7.1)
Dry Skin	33 (9.3)	14 (4.0)
Pruritus	27 (7.6)	18 (5.1)
METABOLISM AND NUTRITION DISORDERS		
Anorexia	55 (15.6)	34 (9.7)
Hypokalemia	48 (13.6)	21 (6.0)
Hypocalcemia	31 (8.8)	10 (2.9)
Appetite Decreased	24 (6.8)	14 (4.0)
Dehydration	23 (6.5)	15 (4.3)
Hypomagnesaemia	24 (6.8)	10 (2.9)
INVESTIGATIONS		
Weight Decreased	69 (19.5)	52 (14.9)
EYE DISORDERS		
Blurred vision	61 (17.3)	40 (11.4)
VASCULAR DISORDERS		
Deep vein thrombosis [%]	33 (9.3)	15 (4.3)
Hypertension	28 (7.9)	20 (5.7)
Hypotension	25 (7.1)	15 (4.3)

Table 5: Grade 3/4 Adverse Reactions Reported in ≥2% Patients and With a ≥1% Difference in Proportion of Patients Between the Lenalidomide/Dexamethasone and Placebo/Dexamethasone groups

System Organ Class/ Preferred Term	Lenalidomide/Dex# (n=353) n (%)	Placebo/Dex# (n=350) n (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Neutropenia [%]	118 (33.4)	12 (3.4)
Thrombocytopenia [@]	43 (12.2)	22 (6.3)
Anemia [@]	35 (9.9)	20 (5.7)
Leukopenia	14 (4.0)	1 (0.3)
Lymphopenia	10 (2.8)	4 (1.1)
Febrile Neutropenia [%]	8 (2.3)	0 (0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue	23 (6.5)	17 (4.9)
VASCULAR DISORDERS		
Deep vein thrombosis [%]	29 (8.2)	12 (3.4)
INFECTIONS[$] AND INFESTATIONS		
Pneumonia [@]	30 (8.5)	19 (5.4)
Urinary Tract Infection	5 (1.4)	1 (0.3)
METABOLISM AND NUTRITION DISORDERS		
Hypokalemia	17 (4.8)	5 (1.4)
Hypocalcemia	13 (3.7)	6 (1.7)
Hypophosphatemia	9 (2.5)	0 (0.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Pulmonary embolism[@]	14 (4.0)	3 (0.9)
Respiratory Distress [@]	4 (1.1)	0 (0.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Muscle weakness	20 (5.7)	10 (2.9)
Gastrointestinal disorders		
Diarrhea [@]	11 (3.1)	4 (1.1)
Constipation	7 (2.0)	1 (0.3)
Nausea [@]	6 (1.7)	2 (0.6)
CARDIAC DISORDERS		
Atrial fibrillation [@]	13 (3.7)	4 (1.1)
Tachycardia	6 (1.7)	1 (0.3)
Cardiac Failure Congestive [@]	5 (1.4)	1 (0.3)
NERVOUS SYSTEM DISORDERS		
Syncope	10 (2.8)	3 (0.9)
Dizziness	7 (2.0)	3 (0.9)
EYE DISORDERS		
Cataract	6 (1.7)	1 (0.3)
Cataract Unilateral	5 (1.4)	0 (0.0)
PSYCHIATRIC DISORDER		
Depression	10 (2.8)	6 (1.7)

Table 6: Serious Adverse Events Reported in ≥1% Patients and With a ≥1% Difference in Proportion of Patients Between the Lenalidomide / Dexamethasone and Placebo / Dexamethasone Groups

System Organ Class/ Preferred Term	Lenalidomide/Dex[&] (n=353) n (%)	Placebo/Dex[&] (n=350) n (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Febrile Neutropenia[%]	6 (1.7)	0 (0.0)
VASCULAR DISORDERS		
Deep vein thrombosis[%]	26 (7.4)	11 (3.1)
INFECTIONS[$] AND INFESTATIONS		
Pneumonia [@]	33 (9.3)	21 (6.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Pulmonary embolism[@]	13 (3.7)	3 (0.9)
CARDIAC DISORDERS		
Atrial fibrillation [@]	11 (3.1)	2 (0.6)
Cardiac Failure Congestive [@]	5 (1.4)	0 (0.0)
NERVOUS SYSTEM DISORDERS		
Cerebrovascular accident [@]	7 (2.0)	3 (0.9)
GASTROINTESTINAL DISORDERS		
Diarrhea [@]	6 (1.7)	2 (0.6)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Bone Pain	4 (1.1)	0 (0.0)

For all tables above:
n – Number of Patients
* - All Treatment Emergent AEs with 5% of Patients in Lenalidomide / Dex and at Least 2% Difference in Proportion between the Two Arms (Safety population)
# - All Treatment Emergent Grades 3 and 4 AEs with ⩾ 1% Patients in Lenalidomide / Dex and at Least 1% Difference in Proportion between the Two Arms - (Safety population)
& - All Treatment Emergent Serious AEs with ⩾1% Patients in Lenalidomide / Dex and at Least 1% Difference in Proportion between the Two Arms - (Safety population)
@ - ADRs with Death as an outcome
% - ADRs which were considered to be Life Threatening (if the outcome of the event was death, it is included with death cases)
[^]- All PTs under the MedDRA SMQ of Neuropathy of aperipheral sensory nature will be considered listed
[$] - All PTs under SOC of Infections except for rare infections of Public Health interest will be considered listed
[£]-All All PTs under HLT of Rash will be considered listed
Dex=dexamethasone
Median duration of exposure among patients treated with Lenalidomide/Dexamethasone was 44 weeks while median duration of exposure among patients treated with placebo/Dexamethasone was 23 weeks. This should be taken into consideration when comparing frequency of adverse events between two treatment groups Lenalidomide/Dexamethasone vs. placebo/Dexamethasone.

Clinical Trials Experience in Myelodysplastic Syndromes
A total of 148 patients received at least 1 dose of 10 mg Lenalidomide in the del 5q MDS clinical study. At least one adverse event was reported in all of the 148 patients who were treated with the 10 mg starting dose of Lenalidomide.

Table 7 summarizes the adverse events that were reported in ≥5% of the Lenalidomide treated patients in the del 5q MDS clinical study. Table 8 summarizes the most frequently observed Grade 3 and Grade 4 adverse reactions regardless of relationship to treatment with Lenalidomide. In the single-arm studies conducted, it is often not possible to distinguish adverse events that are drug related and those that reflect the patient's underlying disease.

Table 7: Summary of Adverse Events Reported in ≥5% of the Lenalidomide Treated Patients in del 5q MDS Clinical Study

System organ class/Preferred term [a]	10 mg (N=148)	Overall
Patients with at least one adverse event	148	(100.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Thrombocytopenia	91	(61.5)
Neutropenia	87	(58.8)
Anemia	17	(11.5)
Leukopenia	12	(8.1)
Febrile Neutropenia	8	(5.4)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Pruritus	62	(41.9)
Rash	53	(35.8)
Dry Skin	21	(14.2)
Contusion	12	(8.1)
Night Sweats	12	(8.1)
Sweating Increased	10	(6.8)
Ecchymosis	8	(5.4)
Erythema	8	(5.4)
GASTROINTESTINAL DISORDERS		
Diarrhea	72	(48.6)
Constipation	35	(23.6)
Nausea	35	(23.6)
Abdominal Pain	18	(12.2)
Vomiting	15	(10.1)
Abdominal Pain Upper	12	(8.1)
Dry Mouth	10	(6.8)
Loose Stools	9	(6.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Nasopharyngitis	34	(23.0)
Cough	29	(19.6)
Dyspnea	25	(16.9)
Pharyngitis	23	(15.5)
Epistaxis	22	(14.9)
Dyspnea Exertional	10	(6.8)
Rhinitis	10	(6.8)
Bronchitis	9	(6.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue	46	(31.1)
Pyrexia	31	(20.9)
Edema Peripheral	30	(20.3)
Asthenia	22	(14.9)
Edema	15	(10.1)
Pain	10	(6.8)
Rigors	9	(6.1)
Chest Pain	8	(5.4)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Arthralgia	32	(21.6)
Back Pain	31	(20.9)
Muscle Cramp	27	(18.2)
Pain in Limb	16	(10.8)
Myalgia	13	(8.8)
Peripheral Swelling	12	(8.1)
NERVOUS SYSTEM DISORDERS		
Dizziness	29	(19.6)
Headache	29	(19.6)
Hypoesthesia	10	(6.8)
Dysgeusia	9	(6.1)
Peripheral Neuropathy	8	(5.4)
INFECTIONS AND INFESTATIONS		
Upper Respiratory Tract Infection	22	(14.9)
Pneumonia	17	(11.5)
Urinary Tract Infection	16	(10.8)
Sinusitis	12	(8.1)
Cellulitis	8	(5.4)
METABOLISM AND NUTRITION DISORDERS		
Hypokalemia	16	(10.8)
Anorexia	15	(10.1)
Hypomagnesemia	9	(6.1)
INVESTIGATIONS		
Alanine Aminotransferase Increased	12	(8.1)
PSYCHIATRIC DISORDERS		
Insomnia	15	(10.1)
Depression	8	(5.4)
RENAL AND URINARY DISORDERS		
Dysuria	10	(6.8)
VASCULAR DISORDERS		
Hypertension	9	(6.1)
ENDOCRINE DISORDERS		
Acquired Hypothyroidism	10	(6.8)
CARDIAC DISORDERS		
Palpitations	8	(5.4)

System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Table 8: Most Frequently Observed Grade 3 and 4 Adverse Events [1] Regardless of Relationship to Study Drug Treatment

Preferred term [2]	10 mg (N=148)	
Patients with at least one Grade 3/4 AE	131	(88.5)
Neutropenia	79	(53.4)
Thrombocytopenia	74	(50.0)
Pneumonia	11	(7.4)
Rash	10	(6.8)
Anemia	9	(6.1)
Leukopenia	8	(5.4)
Fatigue	7	(4.7)
Dyspnea	7	(4.7)
Back Pain	7	(4.7)
Febrile Neutropenia	6	(4.1)
Nausea	6	(4.1)
Diarrhea	5	(3.4)
Pyrexia	5	(3.4)
Sepsis	4	(2.7)
Dizziness	4	(2.7)
Granulocytopenia	3	(2.0)
Chest Pain	3	(2.0)
Pulmonary Embolism	3	(2.0)
Respiratory Distress	3	(2.0)
Pruritus	3	(2.0)
Pancytopenia	3	(2.0)
Muscle Cramp	3	(2.0)
Respiratory Tract Infection	2	(1.4)
Upper Respiratory Tract Infection	2	(1.4)
Asthenia	2	(1.4)
Multi-organ Failure	2	(1.4)
Epistaxis	2	(1.4)
Hypoxia	2	(1.4)
Pleural Effusion	2	(1.4)
Pneumonitis	2	(1.4)
Pulmonary Hypertension	2	(1.4)
Vomiting	2	(1.4)
Sweating Increased	2	(1.4)
Arthralgia	2	(1.4)
Pain in Limb	2	(1.4)
Headache	2	(1.4)
Syncope	2	(1.4)

[1] Adverse events with frequency ⩾ 1% in the 10 mg Overall group. Grade 3 and 4 are based on National Cancer Institute Common Toxicity Criteria version 2.
[2] Preferred Terms are coded using the MedDRA dictionary. A patient with multiple occurrences of an AE is counted only once in the Preferred Term category.

DRUG INTERACTIONS
Results from human in vitro metabolism studies and studies show that Lenalidomide is neither metabolized by nor inhibits or induces the cytochrome P450 pathway suggesting that Lenalidomide is not likely to cause or be subject to P450-based metabolic drug interactions in man.
Digoxin - When digoxin was co-administered with Lenalidomide, the Digoxin AUC was not significantly different, however the Digoxin C max was increased by 14 %. Periodic monitoring of digoxin plasma level is recommended during administration of Lenalidomide.

Warfarin - Co-administration of multiple doses of 10 mg of Lenalidomide had no effect on the single dose pharmacokinetics of R- and S-warfarin. Co-administration of single 25-mg dose warfarin had no effect on the pharmacokinetics of total Lenalidomide.
Concomitant Therapies That May Increase the Risk of Thrombosis -

Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as estrogen containing therapies, should be used with caution in multiple myeloma patients receiving Lenalidomide with Dexamethasone.

DOSAGE AND ADMINISTRATION
Multiple Myeloma - The recommended starting dose of HUMIX® is 25 mg once daily orally with water on Days 1-21 of repeated 28-day cycles. The recommended dose of Dexamethasone is 40 mg once daily on Days 1-4, 9-12, and 17-20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg once daily orally on Days 1-4 every 28 days.
Myelodysplastic Syndromes - The recommended starting dose of HUMIX® is 10 mg daily with water. Patients should not break, chew or open the capsules. Treatment is continued or modified based upon clinical and laboratory findings.

Dose Adjustments for Hematologic Toxicities During Multiple Myeloma Treatment
Dose modification guidelines, as summarized below, are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia or other Grade 3 or 4 toxicity judged to be related to HUMIX®.

Platelet counts
Thrombocytopenia in MM

When Platelets	Recommended Course
Fall to < 30,000/mcL	Interrupt HUMIX® treatment, follow CBC weekly
Return to ≥ 30,000/mcL	Restart HUMIX® at 15 mg daily
For each subsequent drop <30,000/mcL	Interrupt HUMIX® treatment
Return to ≥ 30,000/mcL	Resume HUMIX® at 5 mg less than the previous dose. Do not dose below 5 mg daily

Absolute Neutrophil counts (ANC)
Neutropenia in MM

When Neutrophils	Recommended Course
Fall to < 1000/mcL	Interrupt HUMIX® treatment, add G-CSF, follow CBC weekly
Return to ≥ 1,000/mcL and neutropenia is the only toxicity	Resume HUMIX® at 25 mg daily
Return to ≥ 1,000/mcL and if other toxicity	Resume HUMIX® at 15 mg daily
For each subsequent drop < 1,000/mcL	Interrupt HUMIX® treatment
Return to ≥ 1,000/mcL	Resume HUMIX® 5 mg less than the previous dose. Do not dose below 5 mg daily

Other Grade 3 / 4 Toxicities in MM
For other Grade 3/4 toxicities judged to be related to HUMIX®, hold treatment and restart at next lower dose level when toxicity has resolved to Grade 2.

Starting Dose Adjustment for Renal Impairment in MM
Since HUMIX® is primarily excreted unchanged by the kidney, adjustments to the starting dose of HUMIX® are recommended to provide appropriate drug exposure in patients with moderate or severe renal impairment and in patients on dialysis. Based on a pharmacokinetic study in patients with renal impairment due to nonmalignant conditions, HUMIX® starting dose adjustment is recommended for patients with CLcr < 60 mL/min. Non-dialysis patients with creatinine clearances less than 11 mL/min and dialysis patients with creatinine clearances less than 7 mL/min have not been studied. The recommendations for initial starting doses for patients with multiple myeloma (MM) are as follows:

Table 9: Starting Dose Adjustment for Renal Impairment in Multiple Myeloma (Days 1 – 21 of each 28 day cycle)

Category	Renal Function (Cockcroft-Gault)	Dose
Moderate Renal Impairment	CLcr 30-60 mL/min	10 mg Every 24 hours
Severe Renal Impairment	CLcr < 30 mL/min (not requiring dialysis)	15 mg Every 48 hours
End Stage Renal Disease	CLcr < 30 mL/min (requiring dialysis)	5 mg Once daily. On dialysis days, administer the dose following dialysis.

After initiation of HUMIX® therapy, subsequent HUMIX® dose modification should be based on individual patient treatment tolerance, as described elsewhere in this section.

Myelodysplastic Syndromes
The recommended starting dose of HUMIX® is 10 mg daily with water. Patients should not break, chew or open the capsules. Treatment is continued or modified based upon clinical and laboratory findings.

Dose Adjustments for Hematologic Toxicities During MDS Treatment
Patients who are dosed initially at 10 mg and who experience thrombocytopenia should have their dosage adjusted as follows:

Platelet counts
If thrombocytopenia develops WITHIN 4 weeks of starting treatment at 10 mg daily in MDS

If baseline ≥ 100,000/mcL	
When Platelets	**Recommended Course**
Fall to < 50,000/mcL	Interrupt HUMIX® treatment
Return to ≥ 50,000/mcL	Resume HUMIX® at 5 mg daily
If baseline < 100,000/mcL	
When Platelets	**Recommended Course**
Fall to 50% of the baseline value	Interrupt HUMIX® treatment
If baseline ≥ 60,000/mcL and returns to ≥ 50,000/mcL	Resume HUMIX® at 5 mg daily
If baseline < 60,000/mcL and returns to ≥ 30,000/mcL	Resume HUMIX® at 5 mg daily

If thrombocytopenia develops AFTER 4 weeks of starting treatment at 10 mg daily in MDS

When Platelets	Recommended Course
< 30,000/mcL or < 50,000/mcL with platelet transfusions	Interrupt HUMIX® treatment
Return to ≥ 30,000/mcL (without hemostatic failure)	Resume HUMIX® at 5 mg daily

Patients who experience thrombocytopenia at 5 mg daily should have their dosage adjusted as follows:
If thrombocytopenia develops during treatment at 5 mg daily in MDS

When Platelets	Recommended Course
< 30,000/mcL or < 50,000/mcL with platelet transfusions	Interrupt HUMIX® treatment
Return to ≥ 30,000/mcL (without hemostatic failure)	Resume HUMIX® at 5 mg every other day

Patients who are dosed initially at 10 mg and experience neutropenia should have their dosage adjusted as follows:

Absolute Neutrophil counts (ANC)

If neutropenia develops WITHIN 4 weeks of starting treatment at 10 mg daily in MDS
If baseline ANC ≥ 1,000/mcL

When Neutrophils	Recommended Course
Fall to < 750/mcL	Interrupt HUMIX® treatment
Return to ≥ 1,000/mcL	Resume HUMIX® at 5 mg daily

If baseline ANC <1,000/mcL

When Neutrophils	Recommended
Fall to < 500/mcL	Interrupt HUMIX® treatment
Return to ≥ 500/mcL	Resume HUMIX® at 5 mg daily

If neutropenia develops AFTER 4 weeks of starting treatment at 10 mg daily in MDS

When Neutrophils	Recommended Course
< 500/mcL for ≥ 7 days or <500/mcL associated with fever (≥ 38.5°C)	Interrupt HUMIX® treatment
Return to ≥ 500/mcL	Resume HUMIX® at 5 mg daily

Patients who experience neutropenia at 5 mg daily should have their dosage adjusted as follows:
If neutropenia develops during treatment at 5 mg daily in MDS

When Neutrophils	Recommended Course
< 500/mcL for ≥ 7 days or < 500/mcL associated with fever (≥ 38.5°C)	Interrupt HUMIX® treatment
Return to ≥ 500/mcL	Resume HUMIX® at 5 mg every other day

Starting Dose Adjustment for Renal Impairment in MDS
Since Lenalidomide is primarily excreted unchanged by the kidney, adjustments to the starting dose of HUMIX® are recommended to provide appropriate drug exposure in patients with moderate or severe renal impairment and in patients on dialysis. Based on a pharmacokinetic study in patients with renal impairment due to nonmalignant conditions, Lenalidomide starting dose adjustment is recommended for patients with CLcr < 60 mL/min. Non-dialysis patients with creatinine clearances less than 11 mL/min and dialysis patients with creatinine clearances less than 7 mL/min have not been studied. The recommendations for initial starting doses for patients with myelodysplastic syndromes (MDS) are as follows:

Table 10: Starting Dose Adjustment for Renal Impairment in Myelodysplastic Syndromes (Days 1 – 28 of each 28 day cycle)

Category	Renal Function (Cockcroft-Gault)	Dose
Moderate Renal Impairment	CLcr 30-60 mL/min	5 mg Every 24 hours
Severe Renal Impairment	CLcr < 30 mL/min (not requiring dialysis)	5 mg Every 48 hours
End Stage Renal Disease	CLcr < 30 mL/min (requiring dialysis)	5 mg 3 times a week following each dialysis

After initiation of HUMIX® therapy, subsequent HUMIX® dose modification should be based on individual patient treatment tolerance, as described elsewhere in this section.

OVERDOSAGE
No cases of overdose have been reported during the clinical studies.

PRESENTATION
HUMIX® (Lenalidomide capsules) contains hard gelatin capsules of Lenalidomide 5 mg, 10 mg and 25 mg.

STORAGE
Store below 25°C. Protect from light and moisture. Keep out of reach of children

INFORMATION FOR PATIENTS
Lenalidomide may cause serious side effects including:

- Possible birth defects (deformed babies) or death of an unborn baby. Females who are pregnant or who plan to become pregnant must not take Lenalidomide. Lenalidomide is similar to the medicine thalidomide. Thalidomide can cause severe life-threatening birth defects. Lenalidomide has not been tested in pregnant women. Lenalidomide has harmed unborn animals in animal testing.

  Females must not get pregnant:
  - for 4 weeks before starting Lenalidomide
  - while taking Lenalidomide
  - during any breaks (interruptions) in the treatment with Lenalidomide
  - for 4 weeks after stopping Lenalidomide
- Low white blood cells (neutropenia) and low platelets (thrombocytopenia). Lenalidomide causes low white blood cells and low platelets in most patients. A blood transfusion or certain medicines are required if the blood counts drop too low. If being treated for multiple myeloma, blood counts should be checked every 2 weeks for the first 12 weeks and then at least monthly thereafter.
- A higher chance for blood clots in veins and lungs. Lenalidomide can cause symptoms like: shortness of breath, chest pain or arm and leg swelling. A doctor should be consulted if any of these symptoms occur.

References
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2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
3. American Society of Health-System Pharmacists. ASHP Guidelines on Handling Hazardous Drugs: Am J Health-Syst Pharm. 2006;63:1172-1193.
4. Polovich M., White JM, Kelleher LO (eds). Chemotherapy and biotherapy guidelines and recommendations for practice (2nd ed.) 2005. Pittsburgh, PA: Oncology Nursing Society.

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