09/2019

רופא/ה, רוקח/ת נכבד/ה,

ניאופרם שמחה להודיעך על אישורה של תוספת התוויה לתכשירים:

רבלימיד 2.5 מ"ג Hard Capsule טבלייה קשיחה **Revlimid 2.5 mg**
רבלימיד 5 מ"ג Hard Capsule טבלייה קשיחה **Revlimid 5 mg**
רבלימיד 7.5 מ"ג Hard Capsule טבלייה קשיחה **Revlimid 7.5 mg**
רבלימיד 10 מ"ג Hard Capsule טבלייה קשיחה **Revlimid 10 mg**
רבלימיד 15 מ"ג Hard Capsule טבלייה קשיחה **Revlimid 15 mg**
רבלימיד 20 מ"ג Hard Capsule טבלייה קשיחה **Revlimid 20 mg**
רבלימיד 25 מ"ג Hard Capsule טבלייה קשיחה **Revlimid 25 mg**

החומרים הפעילים וכמותם:

Revlimid 2.5 mg: each hard capsule contains 2.5 mg Lenalidomide.
Revlimid 5 mg: each hard capsule contains 5 mg Lenalidomide.
Revlimid 7.5 mg: each hard capsule contains 7.5 mg Lenalidomide.
Revlimid 10 mg: each hard capsule contains 10 mg Lenalidomide.
Revlimid 15 mg: each hard capsule contains 15 mg Lenalidomide.
Revlimid 20 mg: each hard capsule contains 20 mg Lenalidomide.
Revlimid 25 mg: each hard capsule contains 25 mg Lenalidomide.

נוסח ההתוויה החדשה:

Multiple Myeloma
Revlimid is indicated for:
•The maintenance treatment of adult patients with newly diagnosed multiple myeloma (MM) who have undergone autologous stem cell transplantation.
• Previously untreated multiple myeloma in adult patients who are not eligible for transplant.
• In combination with dexamethasone treatment of multiple myeloma patients who have received at least one prior therapy.

Myelodysplastic Syndromes
REVLIMID is indicated for 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.
Revlimid 7.5 mg is not indicated for treatment in MDS.

Mantle Cell Lymphoma
REVLIMID is indicated for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL).

בנוסף בהודעה זו מצוינים השינויים המהווים החמרה. בעלון שינויים נוספים שאינם החמרה.

טקסט שהתווסף מסומן בקו תחתי, טקסט שהוסר מסומן בקו חוצה.

העדכונים העיקריים בעלון לרופא נעשו בסעיפים הבאים:

5. WARNINGS AND PRECAUTIONS
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5.2 Reproductive Risk and Special Prescribing Requirements (Revlimid RMP-PPP)
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Prescriptions for women of childbearing potential can be for a maximum duration of 4 weeks, and prescriptions for all other patients can be for a maximum duration of 12 weeks.

5.3 Other warnings and precautions of use

Hematologic Toxicity

~~REVLIMID can cause significant neutropenia and thrombocytopenia.~~ REVLIMID can cause significant neutropenia and thrombocytopenia. Monitor patients with neutropenia for signs of infection. Advise patients to observe for bleeding or bruising, especially with use of concomitant medication that may increase risk of bleeding. Patients taking REVLIMID should have their complete blood counts assessed periodically as described below [see Dosage and Administration (2.1, 2.2, 2.3)]. Patients should be advised to promptly report febrile episodes and dose reductions may be required. Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products susceptible to induce bleeding.

Patients taking REVLIMID in combination with dexamethasone or as REVLIMID maintenance therapy for MM should have their complete blood counts (CBC) assessed every 7 days (weekly) for the first 2 cycles, on Days 1 and 15 of Cycle 3, and every 28 days (4 weeks) thereafter. A dose interruption and/or dose reduction may be required [see Dosage and Administration (2.1)]. In the MM maintenance therapy trials, Grade 3 or 4 neutropenia was reported in up to 59% of REVLIMID treated patients and Grade 3 or 4 thrombocytopenia in up to 38% of REVLIMID-treated patients [see Adverse Reactions (6.1)].

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~~myeloma~~Patients taking REVLIMID for MCL should have their complete blood counts monitored weekly for the first cycle (28 days), every 2 weeks during cycles 2-4, and then monthly thereafter. Patients may require dose interruption and/or dose reduction. In the MCL trial, Grade 3 or 4 neutropenia was reported in 43% of the patients. Grade 3 or 4 thrombocytopenia was reported in 28% of the patients.

Neutropenia and thrombocytopenia

- NDMM

Newly diagnosed multiple myeloma ~~in~~: patients who have undergone ASCT treated with lenalidomide maintenance The adverse reactions from CALGB 100104 included events reported post-high dose melphalan and ASCT (HDM/ASCT) as well as events from the maintenance treatment period. A second analysis identified events that occurred after the start of maintenance treatment. In IFM 2005-02, the adverse reactions were from the maintenance treatment period only.

Overall, grade 4 neutropenia was observed at a higher frequency in the lenalidomide maintenance arms compared to the placebo maintenance arms in the 2 studies evaluating lenalidomide maintenance in NDMM patients who have undergone ASCT (32.1% vs 26.7% [16.1% vs 1.8% after the start of maintenance treatment] in CALGB 100104 and 16.4% vs 0.7% in IFM 2005-02, respectively). Treatment-emergent AEs of neutropenia leading to lenalidomide discontinuation were reported in 2.2% of patients in CALGB 100104 and 2.4% of patients in IFM 2005-02, respectively. Grade 4 febrile neutropenia was reported at similar frequencies in the lenalidomide maintenance arms compared to placebo maintenance arms in both studies (0.4% vs 0.5% [0.4% vs 0.5% after the start of maintenance treatment] in CALGB 100104 and 0.3% vs 0% in IFM 2005-02, respectively). Patients should be advised to promptly report febrile episodes, a treatment interruption and/or dose reductions may be required (see section 4.2).

Grade 3 or 4 thrombocytopenia was observed at a higher frequency in the lenalidomide maintenance arms compared to the placebo maintenance arms in studies evaluating lenalidomide maintenance in NDMM patients who have undergone ASCT (37.5% vs 30.3% [17.9% vs 4.1% after the start of maintenance treatment] in CALGB 100104 and 13.0% vs 2.9% in IFM 2005-02, respectively). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products susceptible to induce bleeding (see section 4.8, Haemorrhagic disorders).

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- Myelodysplastic Syndromes patients

Patients taking REVLIMID for MDS should have their complete blood counts monitored weekly for the first 8 weeks and at least monthly thereafter.

Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the MDS study. In the 48% of patients who developed Grade 3 or 4 neutropenia, the median time to onset was 42 days (range, 14-411 days), and the median

time to documented recovery was 17 days (range, 2-170 days). In the 54% of patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was 28 days (range, 8-290 days), and the median time to documented recovery was 22 days (range, 5-224 days) [see Boxed Warning and Dosage and Administration (2.2)].

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Infection with or without Neutropenia

Patients with multiple myeloma are prone to develop infections including pneumonia. A higher rate of infections was observed with lenalidomide in combination with dexamethasone than with MPT~~.~~ in patients with NDMM who are not eligible for transplant, and with lenalidomide maintenance compared to placebo in patients with NDMM who had undergone ASCT.

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~~1.1~~ ~~5.4~~ *Venous and Arterial Thromboembolism*

~~Venous thromboembolic events (deep~~

In patients with multiple myeloma, the combination of lenalidomide with dexamethasone is associated with an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) and ~~arterial~~ was seen to a lesser extent with lenalidomide in combination with melphalan and prednisone.

In patients with multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma, treatment with lenalidomide monotherapy was associated with a lower risk of venous thromboembolism (predominantly deep vein thrombosis ~~are increased~~and pulmonary embolism) than in patients with multiple myeloma treated with ~~REVLIMID. A significantly~~lenalidomide in combination therapy

~~In patients with multiple myeloma,~~ the combination of lenalidomide with dexamethasone is associated with an increased risk of ~~DVT (7.4%) and of PE (3.7%) occurred in patients with multiple myeloma who were treated with REVLIMID and dexamethasone therapy compared to patients treated in the placebo and dexamethasone group (3.1%~~ arterial thromboembolism (predominantly myocardial infarction and ~~0.9%) in a clinical trials with varying use of anticoagulant therapies. [*see Boxed Warning and Adverse Reactions (6.1)*].~~

Venous thromboembolism cerebrovascular event) and was seen to a lesser extent with lenalidomide in combination with melphalan and prednisone. The risk of ATE is lower in ~~newly diagnosed~~ patients with multiple myeloma ~~and~~treated with lenalidomide monotherapy than in patients with multiple myeloma treated with lenalidomide in ~~myelodysplastic syndromes.~~

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Consequently, patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). Concomitant administration of erythropoietic agents or previous history of thromboembolic events may also increase thrombotic risk in these patients. Therefore, erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone. A haemoglobin concentration above 12 g/dl should lead to discontinuation of erythropoietic agents.

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, arm or leg swelling. Prophylactic antithrombotic medicines should be recommended, especially in patients with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors.

If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the lenalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of lenalidomide treatment.

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~~5.6~~ *Second Primary Malignancies*

An increase of second primary malignancies (SPM) has been observed in clinical trials in previously treated myeloma patients receiving lenalidomide/dexamethasone (3.98 per 100 person-years) compared to controls (1.38 per 100 person-years). Non-invasive SPM comprise basal cell or squamous cell skin cancers. Most of the invasive SPMs were solid tumour malignancies.

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The increased risk of secondary primary malignancies associated with lenalidomide is relevant also in the context of NDMM after stem cell transplantation. Though this risk is not yet fully characterized, it should be kept in mind when considering and using Revlimid in this setting.

The incidence rate of hematologic malignancies, most notably AML, MDS and B-cell malignancies (including Hodgkin's lymphoma), was 1.31 per 100 person-years for the lenalidomide arms and 0.58 per 100 person-years for the placebo arms (1.02 per 100 person-years for patients exposed to lenalidomide after ASCT and 0.60 per 100 person-years for patients not-exposed to lenalidomide after ASCT). The incidence rate of solid tumour SPMs was 1.36 per 100 person-years for the lenalidomide arms and 1.05 per 100 person-years for the placebo arms (1.26 per 100 person-years for patients exposed to lenalidomide after ASCT and 0.60 per 100 person-years for patients not-exposed to lenalidomide after ASCT).

The risk of occurrence of hematologic SPM must be taken into account before initiating treatment with lenalidomide either in combination with melphalan or immediately following high-dose melphalan and ASCT. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated.

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~~**5.8**~~ *Allergic ~~Reactions~~and severe skin reactions*

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Severe cutaneous reactions including SJS, and TEN and DRESS have been reported with the use of lenalidomide. Patients should be advised of the signs and symptoms of these reactions by their prescribers and should be told to seek medical attention immediately if they develop these symptoms. Lenalidomide must be discontinued for exfoliative or bullous rash, or if SJS, TEN or DRESS is suspected, and should not be resumed following discontinuation for these reactions. Interruption or discontinuation of lenalidomide should be considered for other forms of skin reaction depending on severity. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

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Peripheral neuropathy

Lenalidomide is structurally related to thalidomide, which is known to induce severe peripheral neuropathy. There was no increase in peripheral neuropathy observed with long term use of lenalidomide for the treatment of newly diagnosed multiple myeloma.

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6.1 Clinical Trials Experience in Multiple Myeloma

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Tabulated summary for monotherapy in MM

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○ **Table 1. ADRs reported in clinical trials in patients with multiple myeloma treated with lenalidomide maintenance therapy**

System Organ Class/Preferred Term	**All ADRs/Frequency**	**Grade 3-4 ADRs/Frequency**
Infections and Infestations	Very Common Pneumonias◊, a, Upper respiratory tract infection, Neutropenic infection, Bronchitis◊, Influenza◊, Gastroenteritis◊, Sinusitis, Nasopharyngitis, Rhinitis Common Infection◊, Urinary tract infection◊*, Lower respiratory tract infection, Lung infection	Very Common Pneumonias◊, a, Neutropenic infection Common Sepsis◊, b, Bacteraemia, Lung infection◊, Lower respiratory tract infection bacterial, Bronchitis◊, Influenza◊, Gastroenteritis◊, Herpes zoster◊, Infection◊
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Common Myelodysplastic syndrome◊*	
Blood and Lymphatic System Disorders	Very Common Neutropenia◊, Febrile neutropenia◊, Thrombocytopenia◊, Anemia, Leucopenia◊, Lymphopenia	Very Common Neutropenia◊, Febrile neutropenia◊, Thrombocytopenia◊, Anemia, Leucopenia◊, Lymphopenia Common Pancytopenia◊
Metabolism and Nutrition Disorders	Very Common Hypokalaemia	Common Hypokalaemia, Dehydration
Nervous System Disorders	Very Common Paraesthesia Common	Common Headache

System Organ Class/Preferred Term	All ADRs/Frequency	Grade 3-4 ADRs/Frequency
	Peripheral neuropathy[c]	
Vascular Disorders	Common Pulmonary embolism[◊]*	Common Deep vein thrombosis[◊,d]
Respiratory, Thoracic and Mediastinal Disorders	Very Common Cough Common Dyspnoea[◊], Rhinorrhoea	Common Dyspnoea[◊]
Gastrointestinal Disorders	Very Common Diarrhoea, Constipation, Abdominal pain, Nausea Common Vomiting, Abdominal pain upper	Common Diarrhoea, Vomiting, Nausea
Hepatobiliary Disorders	Very Common Abnormal liver function tests	Common Abnormal liver function tests
Skin and Subcutaneous Tissue Disorders	Very Common Rash, Dry skin	Common Rash, Pruritus
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms Common Myalgia, Musculoskeletal pain	
General Disorders and Administration Site Conditions	Very Common Fatigue, Asthenia, Pyrexia	Common Fatigue, Asthenia

[◊] Adverse reactions reported as serious in clinical trials in patients with NDMM who had undergone ASCT
[*] Applies to serious adverse drug reactions only
[a] "Pneumonias" combined AE term includes the following PTs: Bronchopneumonia, Lobar pneumonia, Pneumocystis jiroveci pneumonia, Pneumonia, Pneumonia klebsiella, Pneumonia legionella, Pneumonia mycoplasmal, Pneumonia pneumococcal, Pneumonia streptococcal, Pneumonia viral, Lung disorder, Pneumonitis
[b] "Sepsis" combined AE term includes the following PTs: Bacterial sepsis, Pneumococcal sepsis, Septic shock, Staphylococcal sepsis
[c] "Peripheral neuropathy" combined AE term includes the following preferred terms (PTs): Neuropathy peripheral, Peripheral sensory neuropathy, Polyneuropathy
[d] "Deep vein thrombosis" combined AE term includes the following PTs: Deep vein thrombosis, Thrombosis, Venous thrombosis

Tabulated summary for combination therapy in MM

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Table ~~1~~2: ADRs reported in clinical studies in patients with multiple myeloma treated with lenalidomide in combination with dexamethasone, or with melphalan and prednisone

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Infections and Infestations	Very Common Pneumonia[◊], Upper respiratory tract infection[◊], Bacterial, viral and fungal infections (including opportunistic infections)[◊], Nasopharyngitis, Pharyngitis, Bronchitis[◊] Common Sepsis[◊], Sinusitis[◊]	Common Pneumonia[◊], Bacterial, viral and fungal infections (including opportunistic infections[◊]), Cellulitis[◊], Sepsis[◊], Bronchitis[◊]
Metabolism and Nutrition Disorders	Very Common Hypokalaemia[◊], Hyperglycaemia, Hypocalcaemia[◊], Decreased appetite, Weight decreased Common Hypomagnesaemia, Hyperuricaemia, Dehydration[◊], Hypercalcaemia[+]	Common Hypokalaemia[◊], Hyperglycaemia[◊], Hypocalcaemia, Diabetes mellitus[◊], Hypophosphataemia, Hyponatraemia[◊], Hyperuricaemia, Gout, Decreased appetite, Weight decreased

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms, Bone pain◊, Musculoskeletal and connective tissue pain and discomfort (including back pain◊), Arthralgia◊ Common Muscular weakness, Joint swelling, Myalgia	Common Muscular weakness, Bone pain◊, Musculoskeletal and connective tissue pain and discomfort (including back pain◊) Uncommon Joint swelling

◊ Adverse reactions reported as serious in clinical trials in patients with multiple myeloma treated with lenalidomide in combination with dexamethasone, or with melphalan and prednisone
+ Applies to serious adverse drug reactions only
* Squamous skin cancer was reported in clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls
** Squamous cell carcinoma of skin was reported in a clinical trial in newly diagnosed myeloma patients with lenalidomide/dexamethasone compared to controls

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6.3 Clinical Trials Experience in Mantle Cell Lymphoma

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Table 5: ADRs reported in clinical trials in patients with mantle cell lymphoma treated with lenalidomide

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Cardiac Disorders		Common Acute mMyocardial infarction (including acute)◊, Cardiac failure

◊Adverse events reported as serious in mantle cell lymphoma clinical trials

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Table 56: ADRs reported in post-marketing use in patients treated with lenalidomide

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Immune System Disorders	Not Known Solid organ transplant rejection	
Skin and Subcutaneous Tissue Disorders		Uncommon Angioedema Rare Stevens-Johnson Syndrome, Toxic epidermal necrolysis Not Known Leukocytoclastic vasculitis, Drug Reaction with Eosinophilia and Systemic Symptoms

…….

7. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy ~~**Category X [see *Boxed Warnings and Contraindications (4.1)*]**~~ *exposure registry*

There is a pregnancy exposure registry that monitors pregnancy outcomes in females exposed to REVLIMID during pregnancy as well as female partners of male patients who are exposed to REVLIMID. This registry is also used to understand the root cause for the pregnancy.

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The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

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Data

Animal data

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Following daily oral administration of lenalidomide from Gestation Day 7 through Gestation Day 20 in pregnant rabbits, fetal plasma lenalidomide concentrations were approximately 20-40% of the maternal Cmax. Following a single oral dose to pregnant rats, lenalidomide was detected in fetal plasma and tissues; concentrations of radioactivity in fetal

tissues were generally lower than those in maternal tissues. These data indicated that lenalidomide crossed the placenta.

8.2 ~~Nursing mothers~~ Lactation

I~~t is not known whether this drug is excreted in human milk.~~Risk summary
There is no information regarding the presence of lenalidomide in human milk, the effects of REVLIMID on the breastfed infant, or the effects of REVLIMID on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from lenalidomide~~, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother~~ advice women not to breastfeed during treatment with REVLIMID.

8.3 Females and males of reproductive potential

Pregnancy Testing
REVLIMID can cause fetal harm when administered during pregnancy [see Use in Specific Populations (8.1)]. Verify the pregnancy status of females of reproductive potential prior to initiating REVLIMID therapy and during therapy. Advise females of reproductive potential that they must avoid pregnancy 4 weeks before therapy, while taking REVLIMID, during dose interruptions and for at least 4 weeks after completing therapy.

Females of reproductive potential must have 2 negative pregnancy tests before initiating REVLIMID. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing REVLIMID. Once treatment has started and during dose interruptions, pregnancy testing for females of reproductive potential should occur weekly during the first 4 weeks of use, then pregnancy testing should be repeated every 4 weeks in females with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her menstrual bleeding. REVLIMID treatment must be discontinued during this evaluation.

Contraception
Females
Females of reproductive potential must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously: one highly effective form of contraception – tubal ligation, IUD, hormonal (birth control pills, injections, hormonal patches, vaginal rings, or implants), or partner's vasectomy, and 1 additional effective contraceptive method – male latex or synthetic condom, diaphragm, or cervical cap. Contraception must begin 4 weeks prior to initiating treatment with REVLIMID, during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of REVLIMID
therapy. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy. Females of reproductive potential should be referred to a qualified provider of contraceptive methods, if needed.

~~1.1~~ Males
Lenalidomide is present in the semen of males who take REVLIMID. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID and for up to 4 weeks after discontinuing REVLIMID, even if they have undergone a successful vasectomy.
Male patients taking REVLIMID must not donate sperm.

~~1.2~~ 8.4 Pediatric use

~~Revlimid should not be used in children and adolescents from birth to less than 18 years because of safety concerns.~~
Safety and effectiveness have not been established in pediatric patients.

8.4~~5~~ Geriatric use

~~REVLIMID has been used~~MM in ~~multiple myeloma (MM) clinical trials in~~ combination: Overall, of the 1613 patients ~~up to 91 years of age.~~ in the NDMM study

~~1. *Newly diagnosed multiple myeloma*~~

~~In patients with newly diagnosed multiple myeloma aged 75 years and older~~ who received ~~lenalidomide, there was a higher incidence of serious adverse reactions and adverse reactions that led to~~ study treatment ~~discontinuation Patients with newly diagnosed multiple myeloma aged~~, 94% (1521 /1613) were 65 years of age or older, while 35% (561/1613) were over 75 years of age. The percentage of patients over age 75 ~~years and older should be carefully assessed before~~was similar between study arms (Rd Continuous: 33%; Rd18: 34%; MPT: 33%). Overall, across all treatment ~~is considered.~~

In clinical trials of newly diagnosed multiple myelomaarms, the frequency in ~~transplant non eligible patients, lenalidomide combined therapy~~most of the AE categories (eg, all AEs, grade 3/4 AEs, serious AEs) was ~~less tolerated~~ higher in ~~patients~~ older (> 75 years of age) than in younger (≤ 75 years of age~~ compared to the younger population. These patients discontinued at a higher rate due to intolerance (~~) subjects. Grade 3 or 4 ~~adverse events and serious adverse events), when compared to patients < 75years.~~AEs in the General Disorders and Administration Site Conditions body system were consistently reported at a higher

Multiple myeloma withfrequency (with a difference of at least 5%) in older subjects than in younger subjects across all treatment arms. Grade 3 or 4 TEAEs in the Infections and Infestations, Cardiac Disorders (including cardiac failure and congestive cardiac failure), Skin and Subcutaneous Tissue Disorders, and Renal and Urinary Disorders (including renal failure) body systems were also reported slightly, but consistently, more frequently (<5% difference), in older subjects than in younger subjects across all treatment arms. For other body systems (e.g., Blood and Lymphatic System Disorders, Infections and Infestations, Cardiac Disorders, Vascular Disorders), there was a less consistent trend for increased frequency of grade 3/4 AEs in older vs younger subjects across all treatment arms Serious AEs were generally reported at a higher frequency in the older subjects than in the younger subjects across all treatment arms.

MM maintenance therapy: Overall, 10% (106/1018) of patients were 65 years of age or older, while no patients were over 75 years of age. Grade 3 or 4 AEs were higher in the REVLIMID arm (more than 5% higher) in the patients 65 years of age or older versus younger patients. The frequency of Grade 3 or 4 AEs in the Blood and Lymphatic System Disorders were higher in the REVLIMID arm (more than 5% higher) in the patients 65 years of age or older versus younger patients. There were not a sufficient number of patients 65 years of age or older in REVLIMID maintenance studies who experienced either a serious AE, or discontinued therapy due to an AE to determine whether elderly patients respond relative to safety differently from younger patients.

- ~~MM after~~ at least one prior therapy:

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Of the 134 patients with MCL enrolled in the MCL trial, 63% were age 65 and over, while 22% of patients were age 75 and over. The overall frequency of adverse events was similar in patients over 65 years of age and in younger patients (98% vs. 100%). The overall incidence of grade 3 and 4 adverse events was also similar in these 2 patient groups (79% vs. 78%, respectively). The frequency of serious adverse events was higher in patients over 65 years of age than in younger patients (55% vs. 41%). No differences in efficacy were observed between patients over 65 years of age and younger patients.

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מצ"ב העלון לרופא כפי שאושר על ידי משרד הבריאות הישראלי.

העלון לרופא נשלח למשרד-הבריאות לצורך העלאתו למאגר התרופות שבאתר משרד-הבריאות וניתן לקבלו מודפס על ידי פנייה לבעל הרישום: ניאופרם בע"מ, רח' השילוח 6, ת.ד. 7063 פתח-תקווה, טל: 03-9373737.

בברכה,

עוז וולך

מנהל רגולציה ורוקח ממונה

ניאופרם סיינטיפיק בע"מ