רופא/ה נכבד/ה
רוקח/ת נכבד/ת

ברצוננו להביא לידיעתכם את העדכון בעלון לרופא של התכשיר **ביולי 2021**:

Bortezomib Taro 3.5 mg

הרכב וחוזק

bortezomib 3.5 mg

התוויה כפי שאושרה בתעודת הרישום:

Bortezomib is indicated for the treatment of patients with multiple myeloma.
Bortezomib is indicated for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy.
Bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.

השינויים העיקריים בעלון לרופא:

4. DOSAGE AND ADMINISTRATION

…

4 3. Posology for Patients with Previously Untreated Mantle Cell Lymphoma (MCL)

…

TABLE 3 - Dose adjustments during treatment for patients with previously untreated mantle cell lymphoma

Toxicity	Dose modification or delay
Haematological toxicity	
≥ Grade 3 neutropenia with fever, Grade 4 neutropenia lasting more than 7 days, a platelet count < 10,000 cells/µL	Bortezomib therapy should be withheld for up to 2 weeks until the patient has an ANC ≥ 750 cells/µL and a platelet count ≥ 25,000 cells/µL. •If, after bortezomib has been held, the toxicity does not resolve, as defined above, then bortezomib must be discontinued. •If toxicity resolves i.e., patient has an ANC ≥ 750 cells/µL and a platelet count ≥ 25,000 cells/µL, bortezomib may be reinitiated at a dose reduced by one dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2).
If platelet count < 25,000 cells/µL or ANC < 750 cells/µL on a bortezomib dosing day (other than	Bortezomib therapy should be withheld**.**

תרו אינטרנשיונל בע"מ
הקיטור 14,
ת.ד. 10347, מפרץ חיפה 2624761
טל: 04-8475700
פקס: 04-8727165

Day 1 of each cycle)	
If several bortezomib doses in consecutive cycles are withheld due to toxicity	Reduce bortezomib dose by one dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2)
Grade ≥ 3 non-hematological toxicities considered to be related to bortezomib	Bortezomib therapy should be withheld until symptoms of the toxicity have resolved to Grade 2 or better. Then, bortezomib may be reinitiated at a dose reduced by one dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2). For bortezomib-related neuropathic pain and/or peripheral neuropathy, hold and/or modify bortezomib as outlined in Table 1.

7. WARNINGS AND PRECAUTIONS

…

7.12 Embryo-fetal Toxicity

Based on the mechanism of action and findings in animals, bortezomib can cause fetal harm when administered to a pregnant woman. Bortezomib administered to rabbits during organogenesis at a dose approximately 0.5 times the clinical dose of 1.3 mg/m^2 based on body surface area caused post-implantation loss and a decreased number of live fetuses *[see Use in Specific Populations (10.1)]*.

Women of reproductive potential should avoid becoming pregnant while being treated with bortezomib.
Advise females of reproductive potential that they must use contraception during treatment with bortezomib and for seven months following treatment. Advise males with female sexual partners of reproductive potential that they must use contraception during treatment with bortezomib and for four months following treatment. If bortezomib is used during pregnancy or if the patient becomes pregnant during bortezomib treatment, the patient should be apprised of the potential risk to the fetus only present in copy *[see Use in Specific Populations (10.1, 10.3), Nonclinical Toxicology (14.1)]*.
…

7.21 Intrathecal Administration

There have been fatal cases of inadvertent intrathecal administration of bortezomib. Bortezomib 3.5 mg powder for solution for injection is for intravenous or subcutaneous use. Bortezomib should not be administered intrathecally.

7.22 Electrocardiogram Investigations

There have been isolated cases of QT-interval prolongation in clinical studies, causality has not been established.

8. ADVERSE REACTIONS

…

Mantle Cell Lymphoma (MCL)

The safety profile of bortezomib in 240 MCL patients treated with bortezomib at 1.3 mg/m^2 in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP) vs

תרו אינטרנשיונל בע"מ
הקיטור 14,
ת.ד. 10347, מפרץ חיפה 2624761
טל: 04-8475700
פקס: 04-8727165

242 patients treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP] was relatively consistent to that observed in patients with multiple myeloma with main differences described below. Additional adverse drug reactions identified associated with the use of the combination therapy (VcR-CAP) were hepatitis B infection (< 1%) and myocardial ischaemia (1.3%). The similar incidences of these events in both treatment arms, indicated that these adverse drug reactions are not attributable to bortezomib alone. Notable differences in the MCL patient population as compared to patients in the multiple myeloma studies were a ≥ 5% higher incidence of the haematological adverse reactions (neutropenia, thrombocytopenia, leukopenia, anemia, lymphopenia), peripheral sensory neuropathy, hypertension, pyrexia, pneumonia, stomatitis, and hair disorders.

Adverse drug reactions identified as those with a ≥ 1% incidence, similar or higher incidence in the VcR-CAP arm and with at least a possible or probable causal relationship to the components of the VcR-CAP arm, are listed in Table 12 below. Also included are adverse drug reactions identified in the VcR-CAP arm that were considered by investigators to have at least a possible or probable causal relationship to bortezomib based on historical data in the multiple myeloma studies.

Adverse reactions are listed below by system organ class and frequency grouping. Frequencies are defined as: Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (< 1/10,000), Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Table 12 has been generated using Version 16 of the MedDRA.

TABLE 12: Adverse Reactions in Patients with Mantle Cell Lymphoma Treated with VcR-CAP in a Clinical Trial

Body System	Incidence	Adverse reaction
Infections and infestations	Very Common	Pneumonia*
	Common	Sepsis (inc septic shock)*, Herpes zoster (inc disseminated & ophthalmic), Herpes virus infection*, Bacterial infections*, Upper/lower respiratory tract infection*, Fungal infection*, Herpes simplex*
	Uncommon	Hepatitis B, Infection*, Bronchopneumonia
Blood and Lymphatic System Disorders	Very Common	Thrombocytopenia*, Febrile neutropenia, Neutropenia*, Leukopenia*, Anemia*, Lymphopenia*
	Uncommon	Pancytopenia*
	Common	Hypersensitivity*
Immune System Disorders	Anaphylactic reaction	Anaphylactic reaction
Metabolism and Nutrition Disorders	Very Common	Decreased appetite
	Common	Hypokalaemia*, Blood glucose abnormal*, Hyponatraemia*, Diabetes mellitus*, Fluid

תרו אינטרנשיונל בע"מ
הקיטור 14,
ת.ד. 10347, מפרץ חיפה 2624761
טל: 04-8475700
פקס: 04-8727165

Body System	Incidence	Adverse reaction
		retention
	Uncommon	Tumour lysis syndrome
Psychiatric Disorders	Common	Sleep disorders and disturbances*
Nervous System Disorders	Very Common	Peripheral sensory neuropathy, Dysaesthesia*, Neuralgia*
	Common	Neuropathies*, Motor neuropathy*, Loss of consciousness (inc syncope), Encephalopathy*, Peripheral sensorimotor neuropathy, Dizziness*, Dysgeusia*, Autonomic neuropathy
	Uncommon	Autonomic nervous system imbalance
Eye Disorders	Common	Vision abnormal*
Ear and Labyrinth Disorders	Common	Dysacusis (inc tinnitus)*
	Uncommon	Vertigo*, Hearing impaired (up to and inc deafness)
Cardiac Disorders	Common	Cardiac fibrillation (inc atrial), Arrhythmia*, Cardiac failure (inc left and right ventricular)*, Myocardial ischaemia, Ventricular dysfunction*
	Uncommon	Cardiovascular disorder (inc cardiogenic shock)
Vascular Disorders	Common	Hypertension*, Hypotension*, Orthostatic hypotension
Respiratory, Thoracic and Mediastinal Disorders	Common	Dyspnoea*, Cough*, Hiccups
	Uncommon	Acute respiratory distress syndrome, Pulmonary embolism, Pneumonitis, Pulmonary hypertension, Pulmonary oedema (inc acute)
Gastrointestinal Disorders	Very Common	Nausea and vomiting symptoms*, Diarrhea*, Stomatitis*, Constipation
	Common	Gastrointestinal haemorrhage (inc mucosal)*, Abdominal distension, Dyspepsia, Oropharyngeal pain*, Gastritis*, Oral ulceration*, Abdominal discomfort, Dysphagia, Gastrointestinal inflammation*, Abdominal pain (inc gastrointestinal and splenic pain)*, Oral disorder*
	Uncommon	Colitis (inc clostridium difficile)*
Hepatobiliary Disorders	Common	Hepatotoxicity (inc liver disorder)

תרו אינטרנשיונל בע"מ
הקיטור 14,
ת.ד. 10347, מפרץ חיפה 2624761
טל: 04-8475700
פקס: 04-8727165

Body System	Incidence	Adverse reaction
	Uncommon	Hepatic failure
Skin and Subcutaneous Tissue Disorders	Very Common	Hair disorder*
	Common	Pruritus*, Dermatitis*, Rash*
Musculoskeletal and Connective Tissue Disorders	Common	Muscle spasms*, Musculoskeletal pain*, Pain in extremity
Renal and Urinary Disorders	Common	Urinary tract infection*
General Disorders and Administration Site Conditions	Very Common	Pyrexia*, Fatigue, Asthenia
	Common	Oedema (inc peripheral), Chills, Injection site reaction*, Malaise*
Investigations	Common	Hyperbilirubinaemia*, Protein analyses abnormal*, Weight decreased, Weight increased

*Grouping of more than one MedDRA Preferred Term.

…

Retreatment in Relapsed Multiple Myeloma

A single-arm trial was conducted in 130 patients with relapsed multiple myeloma to determine the efficacy and safety of retreatment with intravenous bortezomib. The safety profile of patients in this trial is consistent with the known safety profile of bortezomib - treated patients with relapsed multiple myeloma as demonstrated in Tables 10, 11, and 13; no cumulative toxicities were observed upon retreatment. The most common adverse drug reaction was thrombocytopenia which occurred in 52% of the patients. The incidence of ≥Grade 3 thrombocytopenia was 24%. Peripheral neuropathy occurred in 28% of patients, with the incidence of ≥Grade 3 peripheral neuropathy reported at 6%.

The incidence of serious adverse reactions was 12.3%. The most commonly reported serious adverse reactions were thrombocytopenia (3.8%), diarrhea (2.3%), and herpes zoster and pneumonia (1.5% each).

Adverse reactions leading to discontinuation occurred in 13% of patients. The reasons for discontinuation included peripheral neuropathy (5%) and diarrhea (3%).

Two deaths considered to be bortezomib-related occurred within 30 days of the last bortezomib dose; one in a patient with cerebrovascular accident and one in a patient with sepsis.

…

Mantle Cell Lymphoma

Antiviral prophylaxis was administered to 137 of 240 patients (57%) in the VcR-CAP arm. The incidence of herpes zoster among patients in the VcR-CAP arm was 10.7% for patients

תרו אינטרנשיונל בע"מ
הקיטור 14,
ת.ד. 10347, מפרץ חיפה 2624761
טל: 04-8475700
פקס: 04-8727165

not administered antiviral prophylaxis compared to 3.6% for patients administered antiviral prophylaxis (see section 7.13).

Hepatitis B Virus (HBV) Reactivation and Infection

HBV infection with fatal outcomes occurred in 0.8% (n=2) of patients in the non-VELCADE treatment group (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP) and 0.4% (n=1) of patients receiving VELCADE in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP). The overall incidence of hepatitis B infections was similar in patients treated with VcR-CAP or with R-CHOP (0.8% vs 1.2% respectively).

In study LYM-3002 in which bortezomib was administered with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CAP), the incidence of peripheral neuropathy in the combination regimens is presented in the table below:

TABLE 14: Incidence of Peripheral neuRopathy in Study LYM-3002 by Toxicity and Treatment discontInuation due to Peripheral Neuropathy

	VcR-CAP (N=240)	R-CHOP (N=242)
Incidence of PN (%)		
All Grade PN	30	29
≥ Grade 2 PN	18	9
≥ Grade 3 PN	8	4
Discontinuation due to PN (%)	2	< 1

VcR-CAP=bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone;
R-CHOP= rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone;
PN=peripheral neuropathy
Peripheral neuropathy included the preferred terms: peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, and peripheral sensorimotor neuropathy

Elderly MCL Patients

42.9% and 10.4% of patients in the VcR-CAP arm were in the range 65-74 years and ≥ 75 years of age, respectively. Although in patients aged ≥ 75 years, both VcR-CAP and R-CHOP were less tolerated, the serious adverse event rate in the VcR-CAP groups was 68%, compared to 42% in the R-CHOP group.

8.2 Postmarketing Experience

…

Eye Disorders: Optic neuropathy, blindness, chalazion/blepharitis

…

Nervous System Disorders: Posterior reversible encephalopathy syndrome (PRES, formerly RPLS), Guillain-Barre syndrome, demyelinating polyneuropathy.

תרו אינטרנשיונל בע"מ
הקיטור 14,
ת.ד. 10347, מפרץ חיפה 2624761
טל: 04-8475700
פקס: 04-8727165

…

9. DRUG INTERACTIONS

During clinical trials, hypoglycemia and hyperglycemia were uncommonly and commonly reported in diabetic patients receiving oral hypoglycemics. Patients on oral antidiabetic agents receiving bortezomib treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetics.

10. USE IN SPECIFIC POPULATIONS

…

10.3 Females and Males of Reproductive Potential

Based on its mechanism of action and findings in animals, bortezomib can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (10.1)]*.

Pregnancy Testing

Conduct pregnancy testing in females of reproductive potential prior to initiating bortezomib treatment.

Contraception

Females

Advise females of reproductive potential to avoid pregnancy and use effective contraception during treatment with bortezomib and for at least seven months after the last dose.

Males

Males with female sexual partners of reproductive potential should use effective contraception during treatment with bortezomib and for at least four months after the last dose.

Infertility

Based on the mechanism of action and findings in animals, bortezomib may have an effect on either male or female fertility *[see Nonclinical Toxicology (14.1)]*.

העלון נשלח למשרד הבריאות לצורך פרסומו במאגר התרופות שבאתר משרד הבריאות www.health.gov.il
וניתן לקבלו מודפס על ידי פנייה לבעל הרישום:
תרו אינטרנשיונל בע"מ, רחוב הקיטור 14, ת.ד 10347 מפרץ חיפה 2624761
ובטלפון 1-800-464664 .

תרו אינטרנשיונל בע"מ
הקיטור 14,
ת.ד. 10347, מפרץ חיפה 2624761
טל: 04-8475700
פקס: 04-8727165