אוקטובר 2021

**רופא/ה, רוקח/ת נכבד/ה,**
**חברת טבע מודיעה על העדכונים הבאים בעלון לרופא של התכשיר:**

| | |
|---|---|
| **Bortez Teva 3.5mg** | **בורטז טבע 3.5 מ"ג** |
| **Powder for solution for injection** | **אבקה להכנת תמיסה להזרקה** |

**Contains:**
*Each vial of Bortez Teva 3.5mg*
*contains 3.5mg of Bortezomib (as a mannitol boronic acid)*

## עדכונים בעלון לרופא

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**התוויה כפי שאושרה בתעודת הרישום:**

Bortez Teva 3.5mg is indicated for the treatment of patients with multiple myeloma.
Bortez Teva 3.5mg is indicated for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy.
Bortez Teva 3.5mg 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.

**ברצוננו להודיע שהעלון לרופא עודכן, בפירוט שלהלן כלולים העדכונים העיקריים בלבד (תוספות מסומנות באדום והסרות מידע כטקסט מחוק):**

**4. DOSAGE AND ADMINISTRATION**
[…]

Bortezomib treatment must be withheld at the onset of any ≥ Grade 3 bortezomib-related non-haematological toxicities (excluding neuropathy) or ≥ Grade 3 haematological toxicities. For dose adjustments, see Table 3 below.

**Table 3: Dose Adjustments During Treatment for Patients with Previously Untreated Mantle Cell lymphoma**

| Toxicity | Posology 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.<br>• If, after bortezomib has been held, the toxicity does not resolve, as defined above, then bortezomib must be discontinued.<br>• 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 counts < 25,000 cells/µL or ANC < 750 cells/µL on a bortezomib dosing day (other than Day 1 of each cycle) | Bortezomib therapy should be withheld |
| 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-haematological 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

[…]

### 7.2 Hypotension

The incidence of hypotension (postural, orthostatic, and hypotension NOS) was 8 %. These events are observed throughout therapy. Patients with a history of syncope, patients receiving medications known to be associated with hypotension, and patients who are

dehydrated may be at increased risk of hypotension. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, and administration of mineralocorticoids and/or sympathomimetics *(see Adverse Reactions (8))*.

**7.3 Cardiac Toxicity**

Acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction have occurred during bortezomib therapy, including reports in patients with no risk factors for decreased left ventricular ejection fraction. Patients with risk factors for, or existing heart disease should be frequently monitored.

In the relapsed multiple myeloma study of bortezomib vs. dexamethasone, the incidence of any treatment-related cardiac disorder was 8% and 5% in the bortezomib and dexamethasone groups, respectively. The incidence of adverse reactions suggestive of heart failure (acute pulmonary edema, pulmonary edema, cardiac failure, congestive cardiac failure, cardiogenic shock,) was ≤ 1% for each individual reaction in the bortezomib group. In the dexamethasone group the incidence was ≤ 1% for cardiac failure and congestive cardiac failure; there were no reported reactions of acute pulmonary edema, pulmonary edema, or cardiogenic shock. There have been isolated cases of QT-interval prolongation in clinical studies; causality has not been established.

[…]

**7.11 Thrombotic Microangiopathy**

Cases, sometimes fatal, of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in the postmarketing setting in patients who received bortezomib. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop bortezomib and evaluate. If the diagnosis of TTP/HUS is excluded, consider restarting bortezomib. The safety of reinitiating bortezomib therapy in patients previously experiencing TTP/HUS is not known.

**7.12 Embryo-fetal Risk**

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/m2 based on body surface area caused postimplantation loss and a decreased number of live fetuses [see Use in Specific Populations (10.1)].

Females 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 [see Use in Specific Populations (10.1, 10.3), Nonclinical Toxicology (14.1)].

[…]

**7.20 Haematological toxicity**

Bortezomib treatment is very commonly associated with haematological toxicities (thrombocytopenia, neutropenia and anaemia). In studies in patients with relapsed multiple myeloma treated with bortezomib and in patients with previously untreated MCL treated with bortezomib in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR CAP), one of the most common haematologic toxicity was transient thrombocytopenia. Platelets were lowest at Day 11 of each cycle of bortezomib treatment and typically recovered to baseline by the next cycle. There was no evidence of cumulative thrombocytopenia. The mean platelet count nadir measured was approximately 40% of baseline in the single agent multiple myeloma studies and 50% in the MCL study. In patients with advanced myeloma the severity of thrombocytopenia was related to pre-treatment platelet count: for baseline platelet counts < 75,000/µl, 90% of 21 patients had a count ≤ 25,000/µl during the study, including 14% < 10,000/µl; in contrast, with a baseline platelet count > 75,000/µl, only 14% of 309 patients had a count ≤ 25,000/µl during the study.

In patients with MCL (study LYM 3002), there was a higher incidence (56.7% versus 5.8%) of Grade ≥ 3 thrombocytopenia in the bortezomib treatment group (VcR CAP) as compared to the non bortezomib treatment group (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R CHOP]). The two treatment groups were similar with regard to the overall incidence of all grade bleeding events (6.3% in the VcR CAP group and 5.0% in the R CHOP group) as well as Grade 3 and higher bleeding events (VcR CAP: 4 patients [1.7%]; R CHOP: 3 patients [1.2%]). In the VcR CAP group, 22.5% of patients received platelet transfusions compared to 2.9% of patients in the R CHOP group.

Gastrointestinal and intracerebral haemorrhage, have been reported in association with bortezomib treatment. Therefore, platelet counts should be monitored prior to each dose of bortezomib. Bortezomib therapy should be withheld when the platelet count is < 25,000/µl or, in the case of combination with melphalan and prednisone, when the platelet count is ≤ 30,000/µl (see section 5.3). Potential benefit of the treatment should be carefully weighed against the risks, particularly in case of moderate to severe thrombocytopenia and risk

factors for bleeding.

Complete blood counts (CBC) with differential and including platelet counts should be frequently monitored throughout treatment with bortezomib. Platelet transfusion should be considered when clinically appropriate (see section 4.3).

In patients with MCL, transient neutropenia that was reversible between cycles was observed, with no evidence of cumulative neutropenia. Neutrophils were lowest at Day 11 of each cycle of bortezomib treatment and typically recovered to baseline by the next cycle. In study LYM 3002, colony stimulating factor support was given to 78% of patients in the VcR CAP arm and 61% of patients in the R CHOP arm. Since patients with neutropenia are at increased risk of infections, they should be monitored for signs and symptoms of infection and treated promptly. Granulocyte colony stimulating factors may be administered for haematologic toxicity according to local standard practice. Prophylactic use of granulocyte colony stimulating factors should be considered in case of repeated delays in cycle administration (see section 4.3).

**7.21 Intrathecal administration**

There have been fatal cases of inadvertent intrathecal administration of bortezomib. bortezomib 1 mg powder for solution for injection is for intravenous use only, while 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**

[…]

**Table 10: Most Commonly Reported Adverse reactions (≥ 10%), with Grade 3 and ≥ 4 Intensity in the Relapsed Multiple Myeloma Study (N=221) of Bortezomib Subcutaneous vs Intravenous**

| | Subcutaneous (n=147) | | | Intravenous (n= 74) | | |
|---|---|---|---|---|---|---|
| **Body System Adverse Reaction** | **Total n (%)** | **Toxicity grade, n (%) 3** | **≥4** | **Total n (%)** | **Toxicity grade, n (%) 3** | **≥4** |
| **Blood and lymphatic system disorders** | | | | | | |
| Anemia | 28(19) | 8 (5) | 0 | 17 (23) | 3 (4) | 0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Leukopenia | 26 (18) | 8 (5) | 0 | 15 (20) | 4 (5) | 1 (1) |
| Neutropenia | 34 (23) | 15 (10) | 4 (3) | 20 (27) | 10 (14) | 3 (4) |
| Thrombocytopenia | 44 (30) | 7 (5) | 5 (3) | 25 (34) | 7 (9) | 5 (7) |
| **Gastrointestinal disorders** | | | | | | |
| Diarrhea | 28 (19) | 1 (1) | 0 | 21 (28) | 3 (4) | 0 |
| Nausea | 24 (16) | 0 | 0 | 10 (14) | 0 | 0 |
| Vomiting | 13 (9) | 3 (2) | 0 | 8 (11) | 0 | 0 |
| **General disorders and administration site conditions** | | | | | | |
| Asthenia | 10 (7) | 1 (1) | 0 | 12 (16 ) | 4 (5) | 0 |
| Fatigue | 11 (7) | 3 (2) | 0 | 11 (15) | 3 (4) | 0 |
| Pyrexia | 18(12) | 0 | 0 | 6 (8) | 0 | 0 |
| **Nervous system disorders** | | | | | | |
| Neuralgia | 34 (23) | 5 (3) | 0 | 17 (23) | 7 (9) | 0 |
| Peripheral neuropathies NEC* | 55 (37) | 8 (5) | 1 (1) | 37 (50) | 10 (14) | 1 (1) |

Note: Safety population: 147 patients in the subcutaneous treatment group and 74 patients in the intravenous treatment group who received at least 1 dose of study medication.

* Represents High Level Term Peripheral Neuropathies NEC.

[…]

**Mantle Cell Lymphoma (MCL)**

The safety profile of bortezomib in 240 MCL patients treated with bortezomib at 1.3 mg/m2 in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR CAP) versus 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 8 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**

| System Organ Class | 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*, Anaemia*, Lymphopenia* |
| | Uncommon | Pancytopenia* |
| Immune system disorders | Common | Hypersensitivity* |
| | Uncommon | Anaphylactic reaction |
| Metabolism and nutrition disorders | Very Common | Decreased appetite |
| | Common | Hypokalaemia*, Blood glucose abnormal*, Hyponatraemia*, Diabetes mellitus*, Fluid 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* |
| | Common | Dysacusis (inc tinnitus)* |

| | | |
|---|---|---|
| Ear and labyrinth disorders | 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*, Diarrhoea*, 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) |
| | 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 not administered antiviral prophylaxis compared to 3.6% for patients administered antiviral prophylaxis (see section 7.13).

[…]

**Hepatitis B Virus (HBV) reactivation and infection**

**Mantle cell lymphoma**

HBV infection with fatal outcomes occurred in 0.8% (n=2) of patients in the non bortezomib treatment group (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R CHOP ) and 0.4% (n=1) of patients receiving bortezomib 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 Post-marketing Experience**

***Eye Disorders:*** optic neuropathy, blindness, chalazion/blepharitis

[…]

***Nervous System Disorders:*** Posterior reversible encephalopathy syndrome (PRES formerly RPLS), Guillain-Barre Syndrome, Demyelinating polyneuropathy

[…]

## 10. USE IN SPECIFIC POPULATIONS

**10.1 Pregnancy**

Risk Summary

Based on its mechanism of action *[see Clinical Pharmacology (13.1)]* findings in animals, Bortezomib can cause fetal harm when administered to a pregnant woman. There are no

studies with the use of Bortezomib in pregnant women to inform drug-associated risks. Bortezomib caused embryo-fetal lethality in rabbits at doses lower than the clinical dose (see data). Advise pregnant women of the potential risk to the fetus.
[…]

**10.2 Lactation**
Risk Summary
There are no data on the presence of bortezomib or its metabolites in human milk, the effects of the drug on the breastfed child, or the effects of the drug on milk production. Because many drugs are excreted in human milk and because the potential for serious adverse reactions in a breastfed child from bortezomib is unknown, advise nursing women not to breastfeed during treatment with bortezomib and for two months after treatment.

**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)].
[…]