VELZOMIB®
Bortezomib 3.5 mg sterile lyophilized powder for solution for IV injection

1. Name of the medicinal product
VELZOMIB® 3.5 mg powder for solution for injection

2. Qualitative and quantitative composition
Each vial contains 3.5 mg bortezomib

3. Pharmaceutical form
Sterile Lyophilized Powder for solution for injection. Each single use vial contains 3.5 mg Bortezomib as a white to off-white cake or powder.

4. Clinical particulars
4.1 Therapeutic indications
VELZOMIB as monotherapy is indicated for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation. VELZOMIB in combination with melphalan and prednisone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant.

4.2 Posology and method of administration
Treatment must be initiated and administered under the supervision of a physician qualified and experienced in the use of chemotherapeutic agents. VELZOMIB must be reconstituted by a healthcare professional. VELZOMIB 3.5 mg powder for solution for injection is available for intravenous administration.

**Posology for monotherapy**
The recommended starting dose of bortezomib is 1.3 mg/m² body surface area twice weekly for two weeks on days 1, 4, 8, and 11, followed by a 10-day rest period on days 12-21. This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of VELZOMIB.
It is recommended that patients with a confirmed complete response receive 2 additional cycles of VELZOMIB beyond a confirmation. It is also recommended that responding patients who do not achieve a complete remission receive a total of 8 cycles of VELZOMIB therapy.
Currently there are limited data concerning re-treatment with VELZOMIB.

*Dose adjustments during treatment and re-initiation of treatment for monotherapy*
VELZOMIB treatment must be withheld at the onset of any Grade 3 non-haematological or any Grade 4 haematological toxicities, excluding neuropathy as discussed below (see also section 4.4). Once the symptoms of the toxicity have
resolved, VELZOMIB treatment may be re-initiated at a 25% reduced dose (1.3 mg/m² reduced to 1.0 mg/m²; 1.0 mg/m² reduced to 0.7 mg/m²). If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of VELZOMIB must be considered unless the benefit of treatment clearly outweighs the risk.

Neuropathic pain and/or peripheral neuropathy

Patients who experience bortezomib-related neuropathic pain and/or peripheral neuropathy are to be managed. Patients with pre-existing severe neuropathy may be treated with VELZOMIB only after careful risk/benefit assessment.

Special populations

Hepatic impairment

Patients with mild hepatic impairment do not require a dose adjustment and should be treated per the recommended dose. Patients with moderate or severe hepatic impairment should be started on VELZOMIB at a reduced dose of 0.7 mg/m² per injection during the first treatment cycle, and a subsequent dose escalation to 1.0 mg/m² or further dose reduction to 0.5 mg/m² may be considered based on patient tolerability (see Table 1 and sections 4.4 and 5.2).

**Table 1: Recommended starting dose modification for VELZOMIB in patients with hepatic impairment**

<table>
<thead>
<tr>
<th>Grade of hepatic impairment</th>
<th>Bilirubin level</th>
<th>SGOT (AST) levels</th>
<th>Modification of starting dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>≤ 1.0x ULN</td>
<td>&gt; ULN</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>&gt;1.0x–1.5x ULN</td>
<td>Any</td>
<td>None</td>
</tr>
<tr>
<td>Moderate</td>
<td>&gt; 1.5x–3x ULN</td>
<td>Any</td>
<td>Reduce VELZOMIB to 0.7 mg/m² in the first treatment cycle. Consider dose escalation to 1.0 mg/m² or further dose reduction to 0.5 mg/m² in subsequent cycles based on patient tolerability.</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt; 3x ULN</td>
<td>Any</td>
<td></td>
</tr>
</tbody>
</table>

Renal impairment

The pharmacokinetics of bortezomib are not influenced in patients with mild to moderate renal impairment (Creatinine Clearance [CrCL] > 20 ml/min/1.73 m²); therefore, dose adjustments are not necessary for these patients. It is unknown if the pharmacokinetics of bortezomib are influenced in patients with severe renal impairment not undergoing dialysis (CrCL < 20 ml/min/1.73 m²). Since dialysis may reduce bortezomib concentrations, VELZOMIB should be administered after the dialysis procedure (see section 5.2).

Elderly patients

There is no evidence to suggest that dose adjustments are necessary in patients over 65 years of age.
**Pediatric population**
The safety and efficacy of VELZOMIB in children below age 18 have not been established (see sections 5.1 and 5.2).

**Posology for combination therapy**
VELZOMIB is administered in combination with oral melphalan and oral prednisone for nine treatment cycles as shown in Table 2. A 6-week period is considered a treatment cycle. In Cycles 1-4, VELZOMIB is administered twice weekly on days 1, 4, 8, 11, 22, 25, 29 and 32. In Cycles 5-9, VELZOMIB is administered once weekly on days 1, 8, 22 and 29. Melphalan and prednisone should both be given orally on days 1, 2, 3 and 4 of the first week of each cycle. At least 72 hours should elapse between consecutive doses of VELZOMIB.

**Table 2: Recommended posology for VELZOMIB in combination with melphalan and prednisone for patients with previously untreated multiple myeloma**

### Twice weekly VELZOMIB (cycles 1-4)

<table>
<thead>
<tr>
<th>Week</th>
<th>1</th>
<th></th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vz (1.3 mg/m²)</td>
<td>Day 1</td>
<td>--</td>
<td>Day 4</td>
<td>Day 8</td>
<td>Day 11</td>
<td>rest period</td>
<td>Day 22</td>
</tr>
<tr>
<td>M (9 mg/m²)</td>
<td>Day 1</td>
<td>Day 2</td>
<td>Day 3</td>
<td>Day 4</td>
<td>--</td>
<td>--</td>
<td>rest period</td>
</tr>
<tr>
<td>P (60 mg/m²)</td>
<td>Day 1</td>
<td>Day 2</td>
<td>Day 3</td>
<td>Day 4</td>
<td>--</td>
<td>--</td>
<td>rest period</td>
</tr>
</tbody>
</table>

### Once weekly VELZOMIB (cycles 5-9)

<table>
<thead>
<tr>
<th>Week</th>
<th>1</th>
<th></th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vz (1.3 mg/m²)</td>
<td>Day 1</td>
<td>--</td>
<td>--</td>
<td>Day 8</td>
<td>rest period</td>
<td>Day 22</td>
<td>Day 29</td>
</tr>
<tr>
<td>M (9 mg/m²)</td>
<td>Day 1</td>
<td>Day 2</td>
<td>Day 3</td>
<td>Day 4</td>
<td>--</td>
<td>--</td>
<td>rest period</td>
</tr>
<tr>
<td>P (60 mg/m²)</td>
<td>Day 1</td>
<td>Day 2</td>
<td>Day 3</td>
<td>Day 4</td>
<td>--</td>
<td>--</td>
<td>rest period</td>
</tr>
</tbody>
</table>

Vz = VELZOMIB; M = melphalan, P = prednisone
Dose adjustments during treatment and re-initiation of treatment for combination therapy
Prior to initiating a new cycle of therapy:
• Platelet counts should be $\geq 70 \times 10^9/l$ and the absolute neutrophils count should be $\geq 1.0 \times 10^9/l$
• Non-hematological toxicities should have resolved to Grade 1 or baseline.

Method of administration

Intravenous injection
VELZOMIB 3.5 mg reconstituted solution is administered as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with sodium chloride 9 mg/ml (0.9%) solution for injection. At least 72 hours should elapse between consecutive doses of VELZOMIB.

4.3 Contraindications
Hypersensitivity to bortezomib, boron or to any of the excipients.
Acute diffuse infiltrative pulmonary and pericardial disease.

4.4 Special warnings and precautions for use
o Gastrointestinal toxicity
o Hematological toxicity
o Herpes zoster virus reactivation
o Peripheral neuropathy
o Hypotension
o Posterior Reversible Encephalopathy Syndrome (PRES)
o Heart failure
o Electrocardiogram investigations
o Pulmonary disorders
o Renal impairment
o Hepatic impairment
o Tumor lysis syndrome

4.5 Interaction with other medicinal products and other forms of interaction
Bortezomib is metabolized by CYP-450 3A4, 2C19 and 1A2. Therefore, closely monitor patients receiving Bortezomib concomitantly with potent CYP3A4 inhibitor or inducers for toxicities or reduced efficacy. Bortezomib may inhibit CYP2C19 activity and increase exposure to drug that are subtricts for this enzyme.

4.6 Pregnancy and lactation
Pregnancy
Category D, to avoid becoming pregnant while being treated with Bortezomib.

Lactation
It is known whether Bortezomib is excreted in human milk. Bortezomib’s long elimination half-life, low molecular weight and moderate protein bonding suggest that it would be excreted in human milk. Because many drugs are excreted in human milk
and because of the potential for serious adverse reactions in breast-feeding infants from Bortezomib decide whether to discontinue breast-feeding or the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines
VELZOMIB may have a moderate influence on the ability to drive and use machines.

4.8 Undesirable effects
The most commonly reported adverse reactions during treatment with bortezomib are nausea, diarrhea, constipation, vomiting, fatigue, pyrexia, thrombocytopenia, anemia, neutropenia, peripheral neuropathy (including sensory), headache, paraesthesia, decreased appetite, dyspnoea, rash, herpes zoster and myalgia. Serious adverse reactions uncommonly reported during treatment with bortezomib include cardiac failure, tumor lysis syndrome, pulmonary hypertension, PRES, acute diffuse infiltrative pulmonary disorders and rarely autonomic neuropathy.

Table 3: Adverse reactions in patients treated with Bortezomib as single agent or in combination

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Herpes zoster (inc disseminated &amp; ophthalmic), Pneumonia, Infection, Herpes simplex, Fungal infection</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Thrombocytopenia, Neutropenia, Anemia, Leukopenia, Lymphopenia</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite, Electrolyte imbalance, Dehydration, Enzyme abnormality, Hyperuricaemia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Mood altered, Anxiety disorder, Sleep disorder</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Neuropathy peripheral, Peripheral sensory neuropathy, Dysaesthesia, Neuralgia, Headache, Peripheral motor neuropathy, Loss of consciousness (inc syncope), Dizziness, Dysgeusia, Lethargy</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Eye swelling, Vision abnormal, Conjunctivitis, Dry eye</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Cardiac failure, Tachycardia</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypotension, Orthostatic hypotension, Hypertension</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnoea, Epistaxis, Upper/lower respiratory tract infection, Cough</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Vomiting, Diarrhoea, Nausea, Constipation, Abdominal pain (inc gastrointestinal pain), Gastrointestinal hemorrhage (inc mucosal), Dyspepsia, Stomatitis, Abdominal distension, Oropharyngeal pain, Abdominal discomfort, Oral disorder, Flatulence</td>
</tr>
<tr>
<td>----------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Hepatic enzyme abnormality</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash, Urticaria, Pruritus, Erythema, Dermatitis, Dry skin</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal pain, Muscle spasms, Pain in extremity, Muscular weakness</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Renal impairment, Renal failure chronic</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Pyrexia, Fatigue, Asthenia, Oedema (inc peripheral), Chills, Pain, Injection site reaction, Malaise</td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight decreased</td>
</tr>
</tbody>
</table>

### 4.9 Overdose

In patients, overdose more than twice the recommended dose has been associated with the acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes. For preclinical cardiovascular safety pharmacology studies, see section 5.3.

There is no known specific antidote for bortezomib overdose. In the event of an overdose, the patient's vital signs should be monitored and appropriate supportive care given to maintain blood pressure (such as fluids, pressors, and/or inotropic agents) and body temperature.

### 5. Pharmacological properties

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: L01XX32

**Mechanism of action**

Bortezomib is a proteasome inhibitor. It is specifically designed to inhibit the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the turnover of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis and affects multiple signalling cascades within the cell, ultimately resulting in cancer cell death. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types and that cancer cells are more sensitive to the pro-apoptotic effects of proteasome inhibition than normal cells. Bortezomib causes reduction of tumor growth *in vivo* in many preclinical tumor models, including multiple myeloma.
5.2 Pharmacokinetic properties
Protein binding
Protein binding averaged 83% in human plasma.

Metabolism
Bortezomib metabolites are inactive as 26S proteasome inhibitors.

Excretion
The mean elimination half-life (t1/2) of Bortezomib upon multiple dosing ranged from 40-193 hours after the 1mg/m² dose and 76 to 108 hours after the 1.3mg/m² dose.

6. Pharmaceutical particulars

6.1 List of excipients
Mannitol, Nitrogen

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life
Unopened vial
2 years

Reconstituted solution
The reconstituted solution should be used immediately after preparation. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. However, the chemical and physical in-use stability of the reconstituted solution has been demonstrated for 8 hours at 25 °C stored in the original vial and/or a syringe. The total storage time for the reconstituted medicinal product should not exceed 8 hours prior to administration.

6.4 Special precautions for storage
Do not store above 30°C. Keep the vial in the outer carton in order to protect from light. For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container
Clear colorless (10R) vial with a bromobutyl rubber which coated with fluropolymer (copolymer of tetrafluoroethylene and ethylene). Each pack contains 1 single-use vial.

6.6 Special precautions for disposal and other handling
General precautions
Bortezomib is a cytotoxic agent. Therefore, caution should be used during handling and preparation of bortezomib. Use of gloves and other protective clothing to prevent skin contact is recommended.
Aseptic technique must be strictly observed throughout the handling of bortezomib, since it contains no preservative.

Instructions for reconstitution
VELZOMIB must be reconstituted by a healthcare professional.

Intravenous injection
Each 10 ml vial of VELZOMIB must be reconstituted with 3.5 ml of sodium chloride 9 mg/ml (0.9%) solution for injection. Dissolution of the lyophilized powder is completed in less than 2 minutes. After reconstitution, each ml solution contains 1 mg bortezomib. The reconstituted solution is clear and colorless. The reconstituted solution must be inspected visually for particulate matter and discoloration prior to administration. If any discoloration or particulate matter is observed, the reconstituted solution must be discarded.

Disposal
VELZOMIB is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder
Cobel Zist Darou
Tehran - Iran

8. IRC number
1228207129

9. Manufacture by
Oncomed
Karasek 229/1b
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Czech Republic

10. Date of revision of the text
26 Jun 2013