เอกสารกำกับยาภาษาอังกฤษ

1. Product name

BORTEZOMIB ALVOGEN 1 mg powder for solution for injection

BORTEZOMIB ALVOGEN 3.5 mg powder for solution for injection

2. Name and strength of active ingredient (s)

Each vial contains 1 mg bortezomib (as a mannitol boronic ester).

Each vial contains 3.5 mg bortezomib (as a mannitol boronic ester).

After reconstitution, 1 ml of solution for subcutaneous injection contains 2.5 mg bortezomib.

After reconstitution, 1 ml of solution for intravenous injection contains 1 mg bortezomib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

White to off-white cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications (Ref. 3: เอกสารกำกับยาต้นแบบ VELCADE attached p.30)

BORTEZOMIB ALVOGEN as monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone 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 haematopoietic stem cell transplantation.

BORTEZOMIB ALVOGEN 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 haematopoietic stem cell transplantation.

BORTEZOMIB ALVOGEN in combination with dexamethasone, or with dexamethasone and thalidomide, is indicated for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

BORTEZOMIB ALVOGEN 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.

4.2 Posology and method of administration

(Ref. 3: เอกสารกำกับยาต้นแบบ VELCADE attached p.31-36)

Treatment must be initiated under the supervision of a physician experienced in the treatment of cancer patients, however BORTEZOMIB ALVOGEN may be administered by a healthcare professional experienced in use of chemotherapeutic agents. Bortezomib must be reconstituted by a healthcare professional.

Posology for treatment of progressive multiple myeloma (patients who have received at least one prior therapy)

Monotherapy

Bortezomib powder for solution for injection is administered via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11, in a 21-day treatment cycle. This 3-week period is considered a treatment cycle. It is recommended that patients receive 2 cycles of bortezomib following a confirmation of a complete response. It is also recommended that responding patients who do not achieve a complete remission receive a total of 8 cycles of bortezomib therapy. At least 72 hours should elapse between consecutive doses of bortezomib.

Dose adjustments during treatment and re-initiation of treatment for monotherapy
(Ref. 1: Drug Facts and Comparison 2016, p.3879)

Bortezomib 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, bortezomib treatment may be re-initiated at a 25% reduced dose (1.3 mg/m^2 reduced to 1.0 mg/m^2; 1.0 mg/m^2 reduced to 0.7 mg/m^2). If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of bortezomib 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 as presented in Table 1 (see section 4.4). Patients with pre-existing severe neuropathy may be treated with bortezomib only after careful risk/benefit assessment.

Table 1: Recommended posology modifications for bortezomib-related neuropathy*

Severity of neuropathy	**Posology modification**
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) with no pain or loss of function	None
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living (ADL)**)	Reduce bortezomib to 1.0 mg/m^2 or Change bortezomib treatment schedule to 1.3 mg/m^2 once per week
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL***)	Withhold bortezomib treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate [product name] treatment and reduce dose to 0.7 mg/m^2 once per week.
Grade 4 (life-threatening consequences; urgent intervention indicated) and/or severe autonomic neuropathy	Discontinue bortezomib

* Based on posology modifications in Phase II and III multiple myeloma studies and post-marketing experience. Grading based on NCI Common Toxicity Criteria CTCAE v 4.0.

** *Instrumental ADL*: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money, etc;

*** *Self care ADL*: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medicinal products, and not bedridden.

Combination therapy with pegylated liposomal doxorubicin
(Ref. 3: เอกสารกำกับยาต้นแบบ VELCADE attached p.31-32)
Bortezomib powder for solution for injection is administered via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11 in a 21-day treatment cycle. This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of bortezomib.
Pegylated liposomal doxorubicin is administered at 30 mg/m^2 on day 4 of the bortezomib treatment cycle as a 1 hour intravenous infusion administered after the bortezomib injection.

Up to 8 cycles of this combination therapy can be administered as long as patients have not progressed and tolerate treatment. Patients achieving a complete response can continue treatment for at least 2 cycles after the first evidence of complete response, even if this requires treatment for more than 8 cycles. Patients whose levels of paraprotein continue to decrease after 8 cycles can also continue for as long as treatment is tolerated and they continue to respond.

For additional information concerning pegylated liposomal doxorubicin, see the corresponding Summary of Product Characteristics.

Combination with dexamethasone
Bortezomib powder for solution for injection is administered via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11 in a 21 day treatment cycle. This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of bortezomib.

Dexamethasone is administered orally at 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 of the bortezomib treatment cycle.

Patients achieving a response or a stable disease after 4 cycles of this combination therapy can continue to receive the same combination for a maximum of 4 additional cycles.

For additional information concerning dexamethasone, see the corresponding Summary of Product Characteristics.

Dose adjustments for combination therapy for patients with progressive multiple myeloma
For bortezomib dosage adjustments for combination therapy follow dose modification guidelines described under monotherapy above.

Posology for previously untreated multiple myeloma patients not eligible for haematopoietic stem cell transplantation (Ref. 1: Drug Facts and Comparison 2016, p.3879)

(Ref. 2: AHFS Drug Information 2016, attached p. 22)

Combination therapy with melphalan and prednisone
Bortezomib powder for solution for injection is administered via intravenous or subcutaneous injection in combination with oral melphalan and oral prednisone as shown in Table 2. A 6-week period is considered a treatment cycle. In Cycles 1-4, bortezomib is administered twice weekly on days 1, 4, 8, 11, 22, 25, 29 and 32. In Cycles 5-9, bortezomib is administered once weekly on days 1, 8, 22 and 29. At least 72 hours should elapse between consecutive doses of bortezomib.

Melphalan and prednisone should both be given orally on days 1, 2, 3 and 4 of the first week of each bortezomib treatment cycle.

Nine treatment cycles of this combination therapy are administered.

Table 2 Recommended posology for bortezomib in combination with melphalan and prednisone

Twice weekly bortezomib (cycles 1-4)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
B (1.3 mg/m$^{2)}$	Day 1	--	--	Day 4	Day 8	Day 11	rest period	Day 22	Day 25	Day 29	Day 32	rest period
M (9 mg/m^2) P (60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period
Once weekly bortezomib (cycles 5-9)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
B (1.3 mg/m^2)	Day 1	--	--	--	Day 8		rest period	Day 22		Day 29		rest period
M (9 mg/m^2) P (60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	--		rest period	--				rest period

B=bortezomib; M=melphalan, P=prednisone

Dose adjustments during treatment and re-initiation of treatment for combination therapy with melphalan and prednisone (Ref. 1: Drug Facts and Comparison 2016, p.3879)

Prior to initiating a new cycle of therapy:

- Platelet counts should be ≥ 70 x 10^9/l and the absolute neutrophils count should be ≥ 1.0 x 10^9/l
- Non-haematological toxicities should have resolved to Grade 1 or baseline

Table 3: Posology modifications during subsequent cycles of bortezomib *therapy in combination with melphalan and prednisone*

Toxicity	**Posology modification or delay**
Haematological toxicity during a cycle • If prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25% in the next cycle.
• If platelet counts ≤ 30 x 10^9/l or ANC ≤ 0.75 x 10^9/l on a bortezomib dosing day (other than Day 1)	Bortezomib therapy should be withheld
• If several bortezomib doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration)	Bortezomib dose should be reduced by 1 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	Bortezomib therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, bortezomib may be reinitiated with one dose level reduction (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.

For additional information concerning melphalan and prednisone, see the corresponding Summary of Product Characteristics.

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Posology for previously untreated multiple myeloma patients eligible for haematopoietic stem cell transplantation (induction therapy) (Ref. 2: AHFS Drug Information 2016, attached p. 22)

Combination therapy with dexamethasone

Bortezomib powder for solution for injection is administered via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11, in a 21-day treatment cycle. This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of bortezomib.

Dexamethasone is administered orally at 40 mg on days 1, 2, 3, 4, 8, 9, 10 and 11 of the bortezomib treatment cycle.

Four bortezomib treatment cycles of this combination therapy are administered.

Combination therapy with dexamethasone and thalidomide

(Ref. 3: เอกสารกำกับยาต้นแบบ VELCADE attached p.33-34)

Bortezomib powder for solution for injection is administered via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11 in a 28 day treatment cycle. This 4-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of bortezomib.

Dexamethasone is administered orally at 40 mg on days 1, 2, 3, 4, 8, 9, 10 and 11 of the bortezomib treatment cycle.

Thalidomide is administered orally at 50 mg daily on days 1-14 and if tolerated the dose is increased to 100 mg on days 15-28, and thereafter may be further increased to 200 mg daily from cycle 2 (see Table 4).

Four treatment cycles of this combination are administered. It is recommended that patients with at least partial response receive 2 additional cycles.

Table 4: Posology for bortezomib combination therapy for patients with previously untreated multiple myeloma eligible for haematopoietic stem cell transplantation

B+ Dx	**Cycles 1 to 4**				
	Week	**1**	**2**	**3**	
	B (1.3 mg/m^2)	Day 1, 4	Day 8, 11	Rest Period	
	Dx 40 mg	Day1, 2, 3, 4	Day 8, 9, 10, 11	-	
B+Dx+T	**Cycle 1**				
	Week	**1**	**2**	**3**	**4**
	B (1.3 mg/m^2)	Day 1, 4	Day 8, 11	Rest Period	Rest Period
	T 50 mg	Daily	Daily	-	-
	T 100 mg[a]	-	-	Daily	Daily
	Dx 40 mg	Day 1, 2, 3, 4	Day 8, 9, 10, 11	-	-
	Cycles 2 to 4[b]				
	B (1.3 mg/m^2)	Day 1, 4	Day 8, 11	Rest Period	Rest Period
	T 200 mg[a]	Daily	Daily	Daily	Daily
	Dx 40 mg	Day 1, 2, 3, 4	Day 8, 9, 10, 11	-	-

B= Bortozemib; Dx=dexamethasone; T=thalidomide

[a] Thalidomide dose is increased to 100 mg from week 3 of Cycle 1 only if 50 mg is tolerated and to 200 mg from cycle 2 onwards if 100 mg is tolerated.

[b] Up to 6 cycles may be given to patients who achieve at least a partial response after 4 cycles.

Dosage adjustments for transplant eligible patients
For bortezomib dosage adjustments, dose modification guidelines described for monotherapy should be followed.
In addition, when bortezomib is given in combination with other chemotherapeutic medicinal products, appropriate dose reductions for these products should be considered in the event of toxicities according to the recommendations in the Summary of Product Characteristics.

Posology for patients with previously untreated mantle cell lymphoma (MCL)
(Ref. 3: เอกสารกำกับยาต้นแบบ VELCADE attached p.34)

Combination therapy with rituximab, cyclophosphamide, doxorubicin and prednisone (BR-CAP)

Bortezomib powder for solution for injection is administered via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m^2 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. Six bortezomib cycles are recommended, although for patients with a response first documented at cycle 6, two additional bortezomib cycles may be given. At least 72 hours should elapse between consecutive doses of bortezomib.

The following medicinal products are administered on day 1 of each bortezomib 3 week treatment cycle as intravenous infusions: rituximab at 375 mg/m^2, cyclophosphamide at 750 mg/m^2 and doxorubicin at 50 mg/m^2.

Prednisone is administered orally at 100 mg/m^2 on days 1, 2, 3, 4 and 5 of each bortezomib treatment cycle.

Dose adjustments during treatment for patients with previously untreated mantle cell lymphoma
(Ref. 3: เอกสารกำกับยาต้นแบบ VELCADE attached p.34-35)

Prior to initiating a new cycle of therapy:

- Platelet counts should be ≥ 100,000 cells/μL and the absolute neutrophils count (ANC) should be ≥ 1,500 cells/μL
- Platelet counts should be ≥ 75,000 cells/μL in patients with bone marrow infiltration or splenic sequestration
- Haemoglobin ≥ 8 g/dL
- Non-haematological toxicities should have resolved to Grade 1 or baseline.

Bortezomib treatment must be withheld at the onset of any ≥ Grade 3 bortezomib-related non-haematological toxicities (excluding neuropathy) or ≥ Grade 3 haematological toxicities (see also section 4.4). For dose adjustments, see Table 5 below.
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. Platelet transfusion for the treatment of thrombocytopenia should be considered when clinically appropriate.

Table 5: 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. • 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 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
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.

In addition, when bortezomib is given in combination with other chemotherapeutic medicinal products, appropriate dose reductions for these medicinal products should be considered in the event of toxicities, according to the recommendations in the respective Summary of Product Characteristics.

Special populations

Elderly

There is no evidence to suggest that dose adjustments are necessary in patients over 65 years of age with multiple myeloma or with mantle cell lymphoma.

There are no studies on the use of bortezomib in elderly patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation. Therefore no dose recommendations can be made in this population.

In a study in previously untreated mantle cell lymphoma patients, 42.9% and 10.4% of patients exposed to bortezomib were in the range 65-74 years and ≥ 75 years of age, respectively. In patients aged ≥ 75 years, both regimens, BR-CAP as well as R-CHOP, were less tolerated (see section 4.8).

Hepatic impairment (Ref. 1: Drug Facts and Comparison 2016, p.3880)

(Ref. 2: AHFS Drug Information 2016, attached p. 23)

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 bortezomib at a reduced dose of 0.7 mg/m^2 per injection during the first treatment cycle, and a subsequent dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 may be considered based on patient tolerability (see Table 6 and sections 4.4 and 5.2).

Table 6: Recommended starting dose modification for bortezomib in patients with hepatic impairment

Grade of hepatic impairment*	**Bilirubin level**	**SGOT (AST) levels**	**Modification of starting dose**
Mild	≤ 1.0 x ULN	> ULN	None
	> 1.0 x-1.5x ULN	Any	None
Moderate	> 1.5 x-3x ULN	Any	Reduce bortezomib to 0.7 mg/m^2 in the first treatment cycle. Consider dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.
Severe	> 3 x ULN	Any	

Abbreviations: SGOT=serum glutamic oxaloacetic transaminase; AST=aspartate aminotransferase; ULN=upper limit of the normal range.
* Based on NCI Organ Dysfunction Working Group classification for categorising hepatic impairment (mild, moderate, severe).

Renal impairment (Ref. 2: AHFS Drug Information 2016, attached p. 27)
(Ref. 3: เอกสารกำกับยาต้นแบบ VELCADE attached p.36)

The pharmacokinetics of bortezomib are not influenced in patients with mild to moderate renal impairment (Creatinine Clearance [CrCL] > 20 ml/min/1.73 m^2); 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 m^2). Since dialysis may reduce bortezomib concentrations, bortezomib should be administered after the dialysis procedure (see section 5.2).

Paediatric population (Ref. 3: เอกสารกำกับยาต้นแบบ VELCADE attached p.27)

The safety and efficacy of bortezomib in children below 18 years of age have not been established (see sections 5.1 and 5.2). Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Method of administration (Ref. 3: เอกสารกำกับยาต้นแบบ VELCADE attached p.36)

BORTEZOMIB ALVOGEN 1 mg powder for solution for injection is available for intravenous administration only.
BORTEZOMIB ALVOGEN 3.5 mg powder for solution for injection is available for intravenous or subcutaneous administration.

BORTEZOMIB ALVOGEN should not be given by other routes. Intrathecal administration has resulted in death.

Intravenous injection
The 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 BORTEZOMIB ALVOGEN.

Subcutaneous injection
BORTEZOMIB ALVOGEN 3.5 mg reconstituted solution is administered subcutaneously through the thighs (right or left) or abdomen (right or left). The solution should be injected subcutaneously, at a 45-90° angle. Injection sites should be rotated for successive injections.

If local injection site reactions occur following BORTEZOMIB ALVOGEN subcutaneous injection, either a less concentrated BORTEZOMIB ALVOGEN solution (BORTEZOMIB ALVOGEN 3.5 mg to be reconstituted to 1 mg/ml instead of 2.5 mg/ml) may be administered subcutaneously or a switch to intravenous injection is recommended.

When BORTEZOMIB ALVOGEN is given in combination with other medicinal products, refer to the Summary of Product Characteristics of these products for instructions for administration.

4.3 Contraindications (Ref. 1: Drug Facts and Comparisons 2016, p.3880)

Hypersensitivity (excluding local reactions) to the active substance, to boron or to any of the Excipients listed in section 6.1.
BORTEZOMIB ALVOGEN is contraindicated for intrathecal administration.

Special warnings and precautions for use

Gastrointestinal toxicity (Ref. 1: Drug Facts and Comparisons 2016, p.3881)

BORTEZOMIB ALVOGEN treatment can cause constipation, diarrhea, nausea and vomiting, sometimes requiring use of antiemetics and antidiarrheal medications. Ileus can occur. Administer fluid and electrolyte replacement to prevent dehydration. Interrupt bortezomib for severe symptoms.

Thrombocytopenia/Neutropenia (Ref. 1: Drug Facts and Comparisons 2016, p.3881)

BORTEZOMIB ALVOGEN is associated with thrombocytopenia and neutropenia that follow a cyclical pattern with nadirs occurring following the last dose of each cycle and typically recovering prior to initiation of the subsequent cycle. The cyclical pattern of platelet and neutrophil decreases and recovery remain consistent in the studies of multiple myeloma and mantle cell lymphoma, and there was no evidence of cumulative thrombocytopenia or neutropenia.

Peripheral Neuropathy (Ref. 1: Drug Facts and Comparisons 2016, p.3880)

BORTEZOMIB ALVOGEN treatment causes a peripheral neuropathy that is predominantly sensory; however, cases of severe sensory and motor peripheral neuropathy have been reported. Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening peripheral neuropathy (including ≥ Grade 3) during treatment with BORTEZOMIB ALVOGEN. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain or weakness.

Patients experiencing new or worsening peripheral neuropathy should undergo neurological evaluation and may require a change in the dose, or schedule of bortezomib.

Hypotension (Ref. 1: Drug Facts and Comparisons 2016, p.3880)

The incidence of hypotension (postural, orthostatic, and hypotension NOS) was 8%. These events are observed throughout therapy. Caution should be used when treating patients with a history of syncope, patients receiving medications known to be associated with hypotension, and patients who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, and administration of mineralocorticoids and/or sympathomimetics.

Posterior Reversible Encephalopathy Syndrome (PRES)

(Ref. 1: Drug Facts and Comparisons 2016, p.3881)

Posterior Reversible Encephalopathy Syndrome (PRES; formerly termed Reversible Posterior Leukoencephalopathy Syndrome (RPLS)) has occurred in patients receiving bortezomib. PRES is a rare, reversible, neurological disorder which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably Magnetic Resonance Imaging (MRI), is used to confirm the diagnosis. In patients developing PRES, discontinue bortezomib. The safety of reinitiating bortezomib therapy in patients previously experiencing PRES is not known.

Cardio effects (Ref. 1: Drug Facts and Comparison 2016, p.3880-3881)

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 closely monitored. In the relapsed multiple myeloma study, 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 (eg. 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.

Electrocardiogram investigations (Ref. 1: Drug Facts and Comparisons 2016, p.3881)

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

Pulmonary effects (Ref. 1: Drug Facts and Comparisons 2016, p.3881)

Acute Respiratory Distress Syndrome (ARDS) and acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, lung infiltration have occurred in patients receiving bortezomib. Some of these events have been fatal.
In a clinical trial, the first two patients given high-dose cytarabine ($2g/m^2$ per day) by continuous infusion with daunorubicin and bortezomib for relapsed acute myelogenous leukemia died of ARDS early in the course of therapy.
There have been reports of pulmonary hypertension associated with bortezomib administration in the absence of left heart failure or significant pulmonary disease.
In the event of new or worsening cardiopulmonary symptoms, consider interrupting bortezomib until a prompt and comprehensive diagnostic evaluation is conducted.

Hepatic function impairment (Ref. 1: Drug Facts and Comparisons 2016, p.3881)

Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; treat these patients with bortezomib at reduced starting dose and closely monitor for toxicities.

Hepatic effects (Ref. 2: AHFS Drug Information 2016, attached p.26)

Acute liver failure has been reported in patients with serious underlying medical conditions who were receiving bortezomib with multiple concomitant medications. Increases in hepatic enzymes concentration, hyperbilirubinemia and hepatitis also have been reported; such changes may be reversible upon discontinuance of bortezomib therapy.

Tumor Lysis Syndrome (Ref. 1: Drug Facts and Comparisons 2016, p.3881)

Tumor lysis syndrome has been reported with bortezomib therapy. Patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. Monitor patients closely and take appropriate precautions.

4.5 Interaction with other medicinal products and other forms of interaction
(Ref. 2: AHFS Drug Information 2016, attached p.28)

Bortezomib is substrate mainly for CYP1A2, CYP3A4 and CYP2C19

CYP3A4 inhibitors (Ref. 2: AHFS Drug Information 2016, attached p.28)

Concomitant administration of BORTEZOMIB ALVOGEN and ketoconazole, a potent CYP3A4 inhibitor, increased the exposure of bortezomib by 35% in 12 patients. Monitor patients for signs of bortezomib toxicity and consider a bortezomib dose reduction if bortezomib must be given in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir).

CYP2C19 inhibitors (Ref. 2: AHFS Drug Information 2016, attached p.28)

Concomitant administration of BORTEZOMIB ALVOGEN and omeprazole, a potent inhibitor of CYP2C19, had no effect on the exposure of bortezomib in 17 patients.

Cytochrome P450 (Ref. 1: Drug Facts and Comparison 2016, p.3881)

Bortezomib is metabolized by CYP-450, 3A4, 2C19 and 1A2. Therefore, closely monitoring patients receiving BORTEZOMIB ALVOGEN concomitantly with potent CYP3A4 inducers. Bortezomib may inhibit CYP2C19 activity and increase exposure to drugs that are substrates for this enzyme.

Melphalan-prednisone (Ref. 2: AHFS Drug Information 2016, attached p.28)

A drug-drug interaction study assessing the effect of melphalan-prednisone on the pharmacokinetics of bortezomib (injected intravenously), showed a mean bortezomib AUC increase of 17% based on data from 21 patients. This is not considered clinically relevant.

Oral antidiabetic agents (Ref. 2: AHFS Drug Information 2016, attached p.28)

In clinical study, hypoglycemia and hyperglycemia have been reported in patient with diabetic mellitus who received BORTEZOMIB ALVOGEN concomitantly with oral antidiabetic agents, blood glucose concentrations should be monitored carefully and adjustment of the dose of antidiabetics as necessary.

4.6 Fertility, pregnancy and lactation

Pregnancy (Ref. 1: Drug Facts and Comparison 2016, p.3881)

Women of reproductive potential should avoid becoming pregnant and should use effective contraceptive during treatment with BORTEZOMIB ALVOGEN.

Lactation (Ref. 1: Drug Facts and Comparison 2016, p.3881)

It is not known whether BORTEZOMIB ALVOGEN is excreted in human milk. Due to the potential for serious adverse reactions in breast-feeding infants, the decision of discontinue BORTEZOMIB ALVOGEN or breast-feeding should take into account the benefits of treatment to the mother.

Pediatric use (Ref. 2: AHFS Drug Information 2016, attached p.27)

Safety and efficacy of bortezomib have not been established in children younger than 18 years of age.

Geriatric use (Ref. 2: AHFS Drug Information 2016, attached p.27)

No overall differences in safety or effectiveness were observed between patients ≥ age 65 and younger patients receiving bortezomib; but greater sensitivity of some older individuals cannot be ruled out.

Patient with renal impairment (Ref. 1: Drug Facts and Comparison 2016, p.3881)

Since dialysis may reduce bortezomib concentrations, bortezomib should be administered after the dialysis procedure.

Patient with hepatic impairment (Ref. 1: Drug Facts and Comparison 2016, p.3881)

The exposure of bortezomib is increased in patients with moderate and severe hepatic impairment. Starting dose should be reduced in those patients.

4.7 Effects on ability to drive and use machines (Ref. 2: AHFS Drug Information 2016, attached p.29)
Bortezomib may be associated with fatigue, dizziness, syncope or orthostatic hypotension. Therefore, patients must be cautious when driving or using machines and should be advised not to drive or operate machinery if they experience these symptoms.

4.8 Undesirable effects
(Ref. 1: Drug Facts and Comparison 2016, p.3883)

Blood and lymphatic system disorders: Anemia, disseminated intravascular coagulation, febrile neutropenia, lymphopenia, leukopenia

Cardiac disorders: Angina pectoris, atrial fibrillation aggravated, atrial flutter, bradycardia, sinus arrest, cardiac amyloidosis, complete atrioventricular block, myocardial ischemia, myocardial infarction, pericarditis, pericardial effusion, *Torsades de pointes*, ventricular tachycardia

Ear and labyrinth disorders: Hearing impaired, vertigo

Eye disorders: Diplopia and blurred vision, conjunctival infection, irritation

Gastrointestinal disorders: Abdominal pain, ascites, dysphagia, fecal impaction, gastroenteritis, gastritis hemorrhagic, hematemesis, hemorrhagic duodenitis, ileus paralytic, large intestinal obstruction, paralytic intestinal obstruction, peritonitis, small intestinal obstruction, large intestinal perforation, stomatitis, melena, pancreatitis acute, oral mucosal petechiae, gastroesophageal reflux

General disorders and administration site conditions: Chills, edema, edema peripheral, injection site erythema, neuralgia, injection site pain, irritation, malaise, phlebitis

Hepatobiliary disorders: Cholestasis, hepatic hemorrhage, hyperbilirubinemia, portal vein thrombosis, hepatitis, liver failure

Immune system disorders: Anaphylactic reaction, drug hypersensitivity, immune complex mediated hypersensitivity, angioedema, laryngeal edema

Infections and infestations: Aspergillosis, bacteremia, bronchitis, urinary tract infection, herpes viral infection, listeriosis, nasopharyngitis, pneumonia, respiratory tract infection, septic shock, toxoplasmosis, oral candidiasis, sinusitis, catheter related infection

Injury, poisoning and procedural complications: Catheter related complication, skeletal fracture, subdural hematoma

Investigations: Weight decreased

Metabolism and nutrition disorders: Dehydration, hypocalcemia, hyperuricemia, hypokalemia, hyperkalemia, hyponatremia, hypernatremia

Musculoskeletal and connective tissue disorders: Arthralgia, back pain, bone pain, myalgia, pain in extremity

Nervous system disorders*:* Ataxia, coma, dizziness, dysarthria, dysesthesia, dysautonomia, encephalopathy, cranial palsy, grand mal convulsion, headache, hemorrhagic stroke, motor dysfunction, neuralgia, spinal cord compression, paralysis, postherpetic neuralgia, transient ischemic attack

Psychiatric disorders*:* Agitation, anxiety, confusion, insomnia, mental status change, psychotic disorder, suicidal ideation

Renal and urinary disorders: Calculus renal, bilateral hydronephrosis, bladder spasm, hematuria, hemorrhagic cystitis, urinary incontinence, urinary retention, renal failure (acute and chronic), glomerular nephritis proliferative

Respiratory, thoracic and mediastinal disorders: Acute respiratory distress syndrome, aspiration pneumonia, atelectasis, chronic obstructive airways disease exacerbated, cough, dysphagia, dyspnea, dyspnea exertional, epistaxis, hemoptysis, hypoxia, lung infiltration, pleural effusion, pneumonitis, respiratory distress, pulmonary hypertension

Skin and subcutaneous tissue disorders*:* Urticaria, face edema, rash (which may be pruritic), leukocytoclastic vasculitis, pruritus.

Vascular disorders*:* Cerebrovascular accident, cerebral hemorrhage, deep venous thrombosis, hypertension, peripheral embolism, pulmonary embolism, pulmonary hypertension

4.9 Overdose (Ref. 3: เอกสารกำกับยาต้นแบบ VELCADE attached p.49)

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: (Ref. 1: Drug Facts and Comparison 2016, p.3880)

Bortezomib is a reversible inhibitor of 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 intracellular concentration of specific proteins, thereby maintaining homeostasis within cells.

Inhibition of the 26S proteasome prevents this targeted proteolysis, which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types in vitro. Bortezomib causes a delay in tumor growth in vivo in nonclinical tumor models, including multiple myeloma.

5.2 Pharmacokinetic properties

Absorption: (Ref. 1: Drug Facts and Comparison 2016, p.3880)

Following intravenous administration of 1 mg/m^2 and 1.3 mg/m^2 doses to 24 patients with multiple myeloma (n=12, per each dose level), the mean maximum plasma concentrations of bortezomib (C_{max}) after the first dose (Day 1) were 57 and 112 ng/mL, respectively. In subsequent doses, when administered twice weekly, the mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1 mg/m^2 dose and 89 to 120 ng/mL for the 1.3 mg/m^2 dose.

Distribution: (Ref. 1: Drug Facts and Comparison 2016, p.3880)

The mean distribution volume of bortezomib ranged from approximately 498 to 1884 L/m^2 following single- or repeat-dose administration of 1 mg/m^2 or 1.3mg/m^2 to patients with multiple myeloma. This suggests bortezomib distributes widely to peripheral tissues. The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100 to 1000 ng/mL.

Metabolism: (Ref. 1: Drug Facts and Comparison 2016, p.3880)

In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolized via cytochrome P450 enzymes 3A4, 2C19, and 1A2. Bortezomib metabolism by CYP 2D6 and 2C9 enzymes is minor. The major metabolic pathway is deboronation to form 2 deboronated metabolites that subsequently undergo hydroxylation to several metabolites.
Deboronated bortezomib metabolites are inactive as 26S proteasome inhibitors. Pooled Plasma data from 8 patients at 10 min and 30 min after dosing indicate that the plasma levels of metabolites are low compared to the parent drug.

Excretion: (Ref. 1: Drug Facts and Comparison 2016, p.3880)

The mean elimination half-life of bortezomib upon multiple dosing ranged from 40 to 193 hours after the 1 mg/m^2 dose and 76 to 108 hours after the 1.3mg/m^2 dose. The mean total body clearances were 102 and 112 L/h following the first dose for doses of 1 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1 and 1.3 mg/m^2, respectively.

5.3 Preclinical safety data (Ref. 3: เอกสารกำกับยาต้นแบบ VELCADE 1 mg attached p.57-58, VELCADE 3.5 mg attached p.59-60)

Bortezomib was positive for clastogenic activity (structural chromosomal aberrations) in the *in vitro* chromosomal aberration assay using Chinese hamster ovary (CHO) cells at concentrations as low as 3.125 µg/ml, which was the lowest concentration evaluated. Bortezomib was not genotoxic when tested in the *in vitro* mutagenicity assay (Ames assay) and *in vivo* micronucleus assay in mice.

Developmental toxicity studies in the rat and rabbit have shown embryo-fetal lethality at maternally toxic doses, but no direct embryo-foetal toxicity below maternally toxic doses. Fertility studies were not performed but evaluation of reproductive tissues has been performed in the general toxicity studies. In the 6-month rat study, degenerative effects in both the testes and the ovary have been observed. It is, therefore, likely that bortezomib could have a potential effect on either male or female fertility. Peri- and postnatal development studies were not conducted.

In multi-cycle general toxicity studies conducted in the rat and monkey, the principal target organs included the gastrointestinal tract, resulting in vomiting and/or diarrhoea; haematopoietic and lymphatic tissues, resulting in peripheral blood cytopenias, lymphoid tissue atrophy and haematopoietic bone marrow hypocellularity; peripheral neuropathy (observed in monkeys, mice and dogs) involving sensory nerve axons; and mild changes in the kidneys. All these target organs have shown partial to full recovery following discontinuation of treatment.

Based on animal studies, the penetration of bortezomib through the blood-brain barrier appears to be limited, if any and the relevance to humans is unknown.

Cardiovascular safety pharmacology studies in monkeys and dogs show that intravenous doses approximately two to three times the recommended clinical dose on a mg/m^2 basis are associated with increases in heart rate, decreases in contractility, hypotension and death. In dogs, the decreased cardiac contractility and hypotension responded to acute intervention with positive inotropic or pressor agents. Moreover, in dog studies, a slight increase in the corrected QT interval was observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E 421)

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
3 years

Reconstituted solution
Chemical and physical in use stability has been demonstrated for 8 hours at 25°C/60%RH in the dark both in a vial and in a polypropylene syringe.

6.4 Special precaution for storage

Keep the vial in the outer carton in order to protect from light.

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

BORTEZOMIB ALVOGEN 1 mg is packed in a colourless type I glass 6R (nominal volume 6 ml) vial with a bromobutyl rubber stopper and a green flip-off cap.

BORTEZOMIB ALVOGEN 3.5 mg is packed in a colourless type I glass 10R (nominal volume 10 ml) vial with a bromobutyl rubber stopper and a blue flip-off cap.

Each pack contains 1 single-use vial.

6.6 Special precautions for disposal and other handling

7. Manufactured by: Oncomed manufacturing a. s.

Karásek 2229/1b, budova 02, 62100 Brno-Řečkovice, Czech Republic

Secondary packed by: GE Pharmaceuticals, Ltd.

Industrial zone Chekanitza – South area, Botevgrad, 2140, Bulgaria

Released by: Synthon Hispania S.L.

Pol. Ind. Las Salinas., c/Castelló, 1 08830 Sant Boi de Llobregat, Barcelona, Spain

Imported by: Alvogen (Thailand) Limited, Bangkok, Thailand.

8. Marketing Authorization Numbers

Reg.No.

9. Date of revision of text

{MM/YYYY}