PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

ONBORT 3,5 mg (powder for solution for injection)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 ml vial contains 3,5 mg bortezomib.

ONBORT contains sugar mannitol (3,5 mg/ml).

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Lyophilised powder for solution for injection. White to off-white cake or powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ONBORT is indicated for:

- Primary treatment of multiple myeloma in combination with melphalan and prednisone.
- Monotherapy for the treatment of patients with multiple myeloma who have received at least one prior therapy and who have progressive disease.
- Treatment of relapsed or refractory mantle cell lymphoma for patients who have received at least 1 prior line of therapy, one of which should have included an anthracycline (or mitoxantrone) and/or rituximab as part of their chemotherapy regimen.

4.2 Posology and method of administration

ONBORT powder for solution for injection is available for:

- Intravenous administration at a concentration of 1 mg/ml (as a 3-5 second bolus injection)

  or

- Subcutaneous administration at a concentration 2,5 mg/ml.

Because each route of administration has a different reconstituted concentration, caution should be used when calculating the volume to be administered.

ONBORT should not be given by other routes. Intrathecal administration has resulted in death (see **Reconstitution instructions below**).

Monotherapy

Recommended dosage

The recommended starting dose of **ONBORT** is 1,3 mg/m^2 body surface area twice weekly for two weeks (days 1, 4, 8 and 11) followed by a 10-day rest period (days 12-21). This 3-week period is considered a treatment cycle. At least 72 hours should lapse between consecutive doses of **ONBORT**.

It is recommended that patients with a confirmed complete response receive 2 additional cycles of **ONBORT** beyond a confirmation. It is also recommended that responding patients who do not achieve a complete remission receive a total of 8 cycles of **ONBORT** therapy.
There are limited data concerning re-treatment with **ONBORT**.

Recommended dosage adjustments during treatment and re-initiation of treatment

ONBORT 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 **section 4.4**). Once the symptoms of the toxicity have resolved, **ONBORT** 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 0,7mg/m^2). If toxicity is not resolved or if it recurs at the lowest dose, discontinuation of **ONBORT** must be considered.

Patients who experience **ONBORT** related neuropathic pain and/or peripheral neuropathy are to be managed as presented in table 1. Patients with pre-existing severe neuropathy may be treated with **ONBORT** only after careful risk/benefit assessment.

Table 1: Recommended* dose modifications for ONBORT related neuropathic pain and /or peripheral

sensory neuropathy

Severity of peripheral neuropathy	**Modification of dose and regimen**
Grade 1 (paraesthesia, weakness and/or loss of reflex) with no pain or loss of function	No action
Grade 1 with pain or grade 2 (interfering with function but not activities of daily living)	Reduce to 1,0 mg/m^2
Grade 2 with pain or grade 3 (interfering with activities of daily living)	Withhold **ONBORT** treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate **ONBORT** treatment and reduce dose to 0,7 mg/m^2 and change treatment schedule to once per week.
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life- threatening or leads to paralysis)	Discontinue **ONBORT**

Special populations

Paediatric patients

ONBORT has not been studied in children and adolescents. Therefore, it should not be used in the paediatric age group until further data become available.

Elderly patients

There is no evidence to suggest that dose adjustments are necessary in the elderly (see **section 4.8**).

Patients with renal impairment

The pharmacokinetics of **ONBORT** are not influenced by the degree of renal impairment. Therefore, dosing adjustments of **ONBORT** are not necessary for patients with renal insufficiency. Since dialysis may reduce **ONBORT** concentrations, **ONBORT** should be administered after the dialysis procedure (see **section 5.2**).

Patients with Hepatic Impairment

Patients with mild hepatic impairment do not require a starting dose adjustment and should be treated per the recommended **ONBORT** dose. Patients with moderate or severe hepatic impairment should be started on **ONBORT** at a reduced dose of 0,7 mg/m^2 per injection during the first 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 tolerance

(see **table 2**).

Table 2: Recommended starting dose modification for ONBORT 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 -1,5 X ULN	Any	None
Moderate	> 1,5 X -3 X ULN	Any	Reduce **ONBORT** to 0,7 mg/m^2 in the first 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).

Combination therapy

Recommended dosage

ONBORT (bortezomib) for injection is administered in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles as shown in Table 3. In cycles 1-4 **ONBORT** is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In cycles 5-9, **ONBORT** is administered once weekly (days 1, 8, 22 and 29).

Table 3: Recommended dosage regimen for ONBORT when used in combination with melphalan and prednisone for patients with previously untreated multiple myeloma:

Twice weekly ONBORT (cycles 1-4)							
Week	1	2	3	4	5	6
Vc (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 **ONBORT** (cycles 5-9)						
Week	1	2	3	4	5	6
Vc (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

Vc = **ONBORT**; m = melphalan; p = prednisone

Dose Management Guidelines for Combination Therapy:

Dose modification and re-initiation of therapy when **ONBORT** is administered in combination with melphalan and prednisone

Prior to initiating a new cycle of therapy:

- Platelet count should be ≥ 70 x 10^9/ℓ and the ANC should be ≥ 1,0 x10^9/ℓ.
- Non-haematological toxicities should have resolved to Grade 1 or baseline.

Table 4: Dose modifications during subsequent cycles:

Toxicity	**Dose modification or delay**
Haematological toxicity during a cycle:	
If prolonged Grade 4 neutropenia or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25 % in the next cycle
If platelet count ≤ 30 x 10^9/ℓ or ANC ≤ 0,75 x 10^9/ℓ on a **ONBORT** dosing day (other than day 1)	**ONBORT** dose should be withheld
If several **ONBORT** doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration	**ONBORT** 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	**ONBORT** therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, **ONBORT** 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 **ONBORT** – related neuropathic pain and/or peripheral neuropathy, hold

	and/or modify **ONBORT** as outlined in Table 1

For additional information concerning melphalan and prednisone, refer to their respective professional inserts.

Method of administration

Administration Precautions

There have been fatal cases of inadvertent intrathecal administration of **ONBORT**.

ONBORT IS FOR INTRAVENOUS USE ONLY.

DO NOT ADMINISTER ONBORT INTRATHECALLY.

Intravenous injection:

The reconstitution solution is administered as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with 0,9 % sodium chloride solution for injection.

Subcutaneous injection:

The reconstituted solution is injection into the thighs (right or left) or abdomen (right or left). Injection sites should be rotated for successive injections.

If local injection site reactions occur following **ONBORT** injection subcutaneously, a less concentrated **ONBORT** solution (1 mg/ml instead of 2,5 mg/ml may be administered subcutaneously, or changed to IV injection.

Reconstitution Instructions

ONBORT is for IV or SC use.

When administered subcutaneously, alternate sites for each injection (thigh or abdomen). New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, red or hard.

ASEPTIC TECHNIQUE MUST BE STRICTLY OBSERVED THROUGHOUT HANDLING OF ONBORT SINCE NO PRESERVATIVE IS PRESENT.

ONBORT is provided as a lyophilised powder in the form of a mannitol boronic ester. When reconstituted, the mannitol ester is in equilibrium with its hydrolysis product, the monomeric boronic acid.

Reconstitution for intravenous administration

Prior to use, the contents of each 5 ml vial must be constituted with 1 mℓ of normal (0,9 %) saline chlorine injection, USP. The contents of each 10 ml vial must be reconstituted with 3,5 ml of normal (0,9 %) saline.

ONBORT must not be mixed with any other medicinal products except for normal (0,9 %) saline, sodium chloride injection, USP.

Table 5: The contents of each vial should be reconstituted only with normal (0,9 %) saline according to the following instructions based on route of administration:

	IV	**SC**
	(3,5 mg bortezomib)	**(3,5 mg bortezomib)**
Volume of diluent (0,9 % Sodium Chloride) added to reconstitute one vial	3,5 ml	1,4 ml
Final concentration after reconstitution (mg/ml)	1,0 mg/ml	2,5 mg/ml

Dissolution is completed in less than 2 minutes. The reconstituted solution is clear and colourless, with a final pH of 4 to 7. The reconstituted solution must be inspected visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the reconstituted product must be discarded.

The reconstituted solution should be used immediately after preparation. If the reconstituted solution is 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 prior to administration, with a maximum of 8 hours in the syringe. Any unused product or waste material should be disposed of appropriately.

4.3 Contraindications

- Hypersensitivity to any of the ingredients of bortezomib, boron, or any of the ingredients of **ONBORT**, including the excipients.
- **ONBORT** is contraindicated for intrathecal administration. Fatal events have occurred with intrathecal administration of **ONBORT**.
- Severe hepatic impairment.
- Pregnancy (see **section 4.6**).

4.4 Special warnings and precautions for use

Treatment must be initiated and administered under the supervision of a medical practitioner and experienced in the use of chemotherapeutic medicines.

There have been fatal cases of inadvertent intrathecal administration of **ONBORT**.

ONBORT is for IV or SC use only.

DO NOT ADMINISTER ONBORT INTRATHECALLY.

Herpes Zoster Virus Reactivation

Medical practitioners should reconsider using antiviral prophylaxis in patients being treated with **ONBORT**. Patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was very common in patients treated with **ONBORT**, melphalan and prednisone (VcMP) Antiviral prophylaxis was administered to 26 % of the patients in the VcMP arm. The incidence of herpes zoster among patients in the VcMP treatment group was 17 % for patients not administered antiviral prophylaxis compared to 3 % for patients administered antiviral prophylaxis.

Patients with mantle cell lymphoma

Safety data for patients with mantle cell lymphoma were evaluated in a phase 2 study, which included 155 patients treated with **ONBORT** at the recommended dose of 1,3 mg/m^2. The safety profile of **ONBORT** in these patients was similar to that observed in patients with multiple myeloma. Notable differences between the two patient populations were that thrombocytopaenia, neutropaenia, anaemia, nausea, vomiting and pyrexia were reported more often in the patients with multiple myeloma than in those with mantle cell lymphoma;

whereas peripheral neuropathy, rash and pruritus were higher among patients with mantle cell lymphoma compared to patients with multiple myeloma.

Based on the integrated safety database from 256 patients with relapsed and/or refractory multiple myeloma, the following special precautions are suggested:

Overall, the safety profile of patients treated with **ONBORT** in monotherapy was similar to that observed in patients treated with **ONBORT** in combination with melphalan and prednisone.

Laboratory Tests

Complete blood counts (CBC) including platelet counts should be frequently monitored throughout treatment with **ONBORT**.

Gastrointestinal toxicity

Gastrointestinal toxicity, including diarrhoea, constipation, nausea and vomiting are very common with **ONBORT** treatment (see **section 4.8**). Reactions usually occur early in treatment (Cycles 1 and 2) and may persist for several cycles. Patients experiencing treatment emergent gastrointestinal toxicity may benefit from administration of anti-emetics and anti-diarrhoeals. Fluid and electrolyte replacement should be administered to prevent or treat dehydration. Cases of ileus have been reported, therefore patients who experience constipation should be closely monitored.

Haematological toxicity

ONBORT treatment is very commonly associated with haematological toxicities (thrombocytopenia and neutropenia). However, febrile neutropenia is an uncommon undesirable effect. The most common haematologic toxicity is transient thrombocytopenia, which generally resolves between treatment cycles. Platelets were lowest at Day 11 of each cycle of **ONBORT** treatment and typically recovered to baseline by the next cycle. The cyclical pattern of platelet decrease and recovery remained consistent over the 8 cycles of twice weekly dosing and there was no evidence of cumulative thrombocytopenia. The mean platelet count nadir measured was approximately 40 % of baseline. Severe bleeding, including CNS and gastrointestinal bleeding, associated with thrombocytopenia, has been reported. In patients with advanced myeloma, the severity of thrombocytopenia was related to pre-treatment platelet count (see **table 6**). Platelet counts should be monitored prior to each dose of **ONBORT**. Therapy should be held when the platelet count is < 25,000/µℓ

and re-initiated at a reduced dose after resolution (see **section 4.8**). Potential benefit of the treatment should be carefully weighed against the risks. Platelet transfusions, red blood cell (RBC) transfusions and administration of growth factors may be utilised in the management of haematologic toxicities. Prophylactic platelet transfusions should be considered in thrombocytopenic patients at high risk of bleeding.

Table 6: The severity of Thrombocytopenia Related to Pre-treatment Platelet Count in the Phase 3 Study Multiple Myeloma Study

Pretreatment Platelet Count	**Number of Patients (N=331)***	**Number of Patients with Platelet Count < 10 000/µℓ**	**Number of Patients with Platelet Count 10 000 – 25 000/µℓ**
≥ 75 000/µℓ	**309**	**8 (3 %)**	**36 (12 %)**
> 50 000/µℓ - 75 000/µℓ	**14**	**2 (14 %)**	**11 (79 %)**
≥ 10 000/µℓ - <50 000/µℓ	**7**	**1 (14 %)**	**5 (71 %)**

* Data for one patient was missing at baseline.

Peripheral Neuropathy

ONBORT treatment causes a peripheral neuropathy that is predominantly sensory. However, cases of severe motor neuropathy with or without sensory 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 **ONBORT**. The incidence of peripheral neuropathy increases early in the treatment and has been observed to peak during cycle 5.

It is recommended that patients be carefully monitored for symptoms of neuropathy such as a burning sensation, hyperaesthesia, hypoaesthesia, paraesthesia, discomfort or neuropathic pain. Patients experiencing new or worsening peripheral neuropathy may require the dose and schedule of **ONBORT** to be modified (see **section 4.2**). Neuropathy has been managed with supportive care and other therapies. Peripheral neuropathy may not be reversible. Improvement in, or resolution of, peripheral neuropathy was reported in 51 % of patients with ≥ Grade 2 peripheral neuropathy in a single agent phase III multiple myeloma study and 71 % of patients

with grade 3 or 4 peripheral neuropathy or peripheral neuropathy leading to discontinuation of treatment in phase II studies, respectively.

In addition to peripheral neuropathy, there may be a contribution of autonomic neuropathy to some adverse reactions such as postural hypotension and severe constipation with ileus. Information on autonomic neuropathy and its contribution to these undesirable effects is limited. The long term outcome of peripheral neuropathy has not been studied in Mantle Cell Lymphoma.

Seizures

Seizures have been uncommonly reported in patients without previous history of seizures or epilepsy. Special care is required when treating patients with any risk factors for seizures.

Hypotension

ONBORT treatment is commonly associated with orthostatic/postural hypotension. Most patients required treatment for their orthostatic hypotension. Patients with orthostatic hypotension experienced syncopal events. The mechanism of this event is unknown although a component may be due to autonomic neuropathy. Autonomic neuropathy may be related to **ONBORT** or **ONBORT** may aggravate an underlying condition such as diabetic neuropathy. Caution is advised when treating patients with a history of syncope receiving medicinal products known to be associated with hypotension; or who are dehydrated due to recurrent diarrhoea or vomiting. Management of orthostatic/postural hypotension is symptomatic and may include adjustment of antihypertensive medicinal products, rehydration or administration of mineralocorticosteroids and/or sympathomimetics. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells.

Cardiac disorders

Development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported. Patients with risk factors for, or existing heart disease should be closely monitored. Fluid retention may be a predisposing factor for signs and symptoms of heart failure.

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

established.

Patients using angiotensin inhibitors, beta-blockers, antihypertensives, calcium channel blockers, angiotensin receptor blockers and diuretics may have a higher incidence of cardiac failure during **ONBORT** treatment.

Pulmonary Disorders

There have been reports of acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, lung infiltration and Acute Respiratory Distress Syndrome (ARDS) in patients receiving **ONBORT**. Some of these events have been fatal. A higher proportion of these events have been reported in Japan. In the event of new or worsening pulmonary symptoms, a prompt diagnostic evaluation should be performed and patients treated appropriately.

Renal Events

Renal complications are frequent in patients with multiple myeloma. Such patients should be monitored closely.

Hepatic Events

Cases of acute liver failure have been reported. Other reported hepatic events include asymptomatic increases in liver enzymes, hyperbilirubinemia and hepatitis. Such changes may be discontinuation of **ONBORT**. There is limited re-challenge information in these patients.

Hepatic Impairment

ONBORT is metabolised by liver enzymes. **ONBORT** exposure is increased in patients with moderate or severe hepatic impairment. These patients should be treated with **ONBORT** at reduced starting doses and closely monitored for toxicities (see **sections 4.2** and **5.2**)

Tumour lysis syndrome

Because **ONBORT** is a cytotoxic substance and can rapidly kill malignant plasma cells, the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. Symptoms of tumour lysis syndrome are weakness, vomiting, cramps, seizure,

oedema and fluid overload, congestive heart failure, dysrrhythmias and syncope. These patients should be reactions monitored closely and appropriate precautions taken.

Amyloidosis

The impact of proteasome inhibition by **ONBORT** on disorders associated with protein accumulation such as amyloidosis is unknown. Caution is advised in these patients.

Potentially immunocomplex-mediated reactions

Potentially immunocomplex-mediated reactions, such as serum-sickness-type reaction, polyarthritis with rash and proliferative glomerulonephritis have been reported uncommonly. **ONBORT** should be discontinued if severe reactions occur.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

There have been reports of RPLS in patients receiving **ONBORT**. RPLS 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 MRI (Magnetic Resonance Imaging), is used to confirm the diagnosis. In patients developing RPLS, discontinue **ONBORT**. The safety of reinitiating **ONBORT** therapy in patients previously experiencing RPLS is not known.

Hepatitis B Virus (HBV) reactivation and infection

When rituximab is used in combination with **ONBORT**, HBV screening must always be performed in patients at risk of infection with HBV before initiation of treatment. Carriers of hepatitis B and patients with a history of hepatitis B must be closely monitored for clinical and laboratory signs of active HBV infection during and following rituximab combination treatment with **ONBORT**. Antiviral prophylaxis should be considered. Refer to the Summary of Product Characteristics of rituximab for more information.

Progressive multifocal leukoencephalopathy (PML)

Very rare cases with unknown causality of John Cunningham (JC) virus infection, resulting in PML and death, have been reported in patients treated with **ONBORT**. Patients diagnosed with PML had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their first dose of

ONBORT. Patients should be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML as part of the differential diagnosis of CNS problems. If a diagnosis of PML is suspected, patients should be referred to a specialist in PML and appropriate diagnostic measures for PML should be initiated. Discontinue **ONBORT** if PML is diagnosed.

Concomitant medicinal products

Patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors. Caution should be exercised when bortezomib is combined with CYP3A4- or CYP2C19 substrates (see **section 4.5**).

Normal liver function should be confirmed and caution should be exercised in patients receiving oral hypoglycemics (see **section 4.5**).

Any special precaution necessary relating to excipients:

ONBORT contains mannitol (3,5 mg/ml). At doses that exceeds 10 g of mannitol per maximum recommended daily dose **ONBORT** may have a mild laxative effect.

4.5 Interaction with other medicines and other forms of interaction

In vitro studies indicate that **ONBORT** is a weak inhibitor of the cytochrome P450 (CYP) isozymes 1A2, 2C9, 2C19, 2D6 and 3A4. Based on the limited contribution (7 %) of CYP2D6 to the metabolism of **ONBORT** the CYP2D6**,** poor metaboliser phenotype is not expected to affect the overall disposition of **ONBORT**.

An interaction study assessing the effect of ketoconazole, a potent CYP3A4 inhibitor, on the pharmacokinetics of **ONBORT**, showed a bortezomib AUC mean increase of 35 %, based on data from 12 patients. Patients should be monitored closely when given **ONBORT** in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir).

In an interaction study assessing the effect of omeprazole, a potent inhibitor of CYP2C19, on the pharmacokinetics of **ONBORT** there was no significant effect on the pharmacokinetics of bortezomib, based on data from 17 patients.

An interaction study assessing the effect of rifampicin, a potent CYP3A4 inducer, on the pharmacokinetics of **ONBORT** showed a mean bortezomib AUC reduction of 45 % based on data from 6 patients. The concomitant use of **ONBORT** with strong CYP3A4 inducers is therefore not recommended, as efficacy may be reduced. Examples of CYP3A4 inducers are rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort. In the same interaction study, the effect of dexamethasone, a weaker CYP3A4 inducer was assessed. There was no significant effect on bortezomib pharmacokinetics based on data from 7 patients.

Concomitant exposure to narcotics may increase the incidence of constipation, nausea and vomiting.

An interaction study assessing the effect of melphalan-prednisone on **ONBORT** showed a 17 % increase in mean bortezomib AUC based on data from 21 patients. This is not considered clinically relevant. Patients on oral antidiabetic medicines receiving **ONBORT** treatment may require close monitoring of the blood glucose levels and adjustment of the dose of their antidiabetic medication. Normal liver function should be confirmed and caution should be exercised in patients receiving oral hypoglycaemic medicines.

4.6 Fertility, pregnancy and lactation

The safety of this preparation in pregnancy and lactation has not been established.

Fertility

Males and females of childbearing capacity should use effective contraceptive measures during treatment and for 3 months following **ONBORT** therapy.

Pregnancy

If **ONBORT** is used during pregnancy, or if the patient becomes pregnant while receiving **ONBORT**, the patient needs to be informed of potential for hazards to the foetus. **ONBORT** should be avoided during pregnancy and women are advised to avoid falling pregnant while on treatment with **ONBORT**.

Lactation

It is not known whether **ONBORT** is excreted in human milk. Because of the potential for serious undesirable effects in breastfed infants from mothers on **ONBORT**, women should not breastfeed their

infants while receiving **ONBORT**.

4.7 Effects on ability to drive and use machines

ONBORT may have a moderate influence on the ability to drive and use machines. **ONBORT** may be associated with fatigue, dizziness, syncope, orthostatic/postural hypotension or blurred vision. Therefore, patients must be cautious when operating machinery, or when driving.

4.8 Undesirable effects

a) Summary of safety profile

Serious adverse reactions uncommonly reported during treatment with **ONBORT** include cardiac failure, tumour lysis syndrome, pulmonary hypertension, posterior reversible encephalopathy syndrome, acute diffuse infiltrative pulmonary disorders and rarely autonomic neuropathy.

The most commonly reported adverse reactions during treatment with **ONBORT** are nausea, diarrhoea, constipation, vomiting, fatigue, pyrexia, thrombocytopenia, anaemia, neutropenia, peripheral neuropathy (including sensory), headache, paraesthesia, decreased appetite, dyspnoea, rash, herpes zoster and myalgia.

b) Tabulated list of adverse reactions

The following undesirable effects included are considered to have at least a possible or probable causal relationship to **ONBORT**.

Infections and infestations:

Frequent: herpes zoster (including disseminated), pneumonia, bronchitis, sinusitis, nasopharyngitis, herpes simplex.

Less frequent: sepsis, bacteraemia, pneumonia pneumococcal, bronchopneumonia, upper and lower respiratory tract infection, catheter related infection, pleural infection, haemophilus infection, cytomegalovirus infection, influenza, infectious, mononucleosis, varicella, urinary tract infection, gastroenteritis, candida infection, fungal infection, post herpetic neuralgia oral candidiasis, blepharitis, infection.

Neoplasms benign, malignant and unspecified (including cysts and polyps):

Less frequent: tumour lysis syndrome (see **section 4.4**).

Blood and the lymphatic system disorders (see section 4.4)

Frequent: thrombocytopenia, neutropenia, anaemia, leukopenia, lymphopenia.

Less frequent: pancytopenia, febrile neutropenia, haemolytic anaemia, thrombocytopenic purpura, lymphadenopathy, disseminated intravascular coagulation.

Immune system disorders:

Less frequent: angioedema, hypersensitivity, immune-complex mediated hypersensitivity, potentially immune-complex-mediated reactions, such as serum-sickness-type reaction, polyarthritis with rash and proliferative glomerulonephritis (see **section 4.4**).

Endocrine disorders:

Less frequent: inappropriate antidiuretic hormone (ADH) secretion.

Metabolism and nutrition disorders:

Frequent: appetite decreased, dehydration, hypokalaemia, hyperglycaemia.

Less frequent: hyperkalaemia, cachexia, hypercalcaemia, hypocalcaemia, hypernatremia, hyponatraemia, hypoglycaemia, hyperuricaemia, vitamin B12 deficiency, appetite increased, hypomagnesaemia, hypophosphataemia.

Psychiatric disorders:

Frequent: confusion, depression, insomnia, anxiety.

Less frequent: agitation, delirium, hallucinations, restlessness, mood swings, mental status changes, sleep disorder, irritability, abnormal dreams.

Nervous system disorders (see section 4.4)

Frequent: peripheral neuropathy, peripheral sensory neuropathy, paraesthesia, headache, polyneuropathy, peripheral neuropathy aggravated, dizziness, (excluding vertigo), dysgeusia, dysaesthesia, hypoesthesia, tremor.

Less frequent: paraplegia, intracranial haemorrhage, subarachnoid haemorrhage convulsions, peripheral motor neuropathy, syncope, paresis, disturbance in attention, increased activity, ageusia, somnolence, migraine, cognitive disorder, jerky movements, postural dizziness, sciatica, mononeuropathy, speech disorder, restless leg syndrome.

Eye disorders:

Frequent: vision blurred, eye pain.

Less frequent: eye haemorrhage, vision abnormal, keratitis sicca, conjunctivitis, eye discharge, photophobia, eye irritation, lacrimation increased, conjunctival hyperaemia, eye swelling.

Ear and labyrinth disorders:

Frequent: vertigo.

Less frequent: deafness, tinnitus, hypoacusis, hearing impaired.

Cardiac disorders:

Less frequent: cardiac arrest, cardiogenic shock, myocardial infarction, unstable angina pectoris, development or exacerbation of congestive heart failure (see **section 4.4**), cardiac failure, ventricular hypokinesia, pulmonary oedema and acute pulmonary oedema, sinus arrest, complete atrioventricular block, tachycardia, sinus tachycardia, supraventricular tachycardia, arrhythmia, atrial fibrillation, palpitations, new onset of decreased left ventricular ejection fraction (see **section 4.4**).

Vascular disorders:

Frequent: hypotension, orthostatic and postural hypotension (see **section 4.4**), phlebitis, haematoma, hypertension.

Less frequent: cerebral haemorrhage, vasculitis, cerebrovascular accident, pulmonary hypertension, petechiae, ecchymosis, purpura, vein discolouration, vein distended, wound haemorrhage, flushing, hot flushes.

Respiratory, thoracic and mediastinal disorders:

Frequent: dyspnoea, exertional dyspnoea, epistaxis, cough, rhinorrhoea.

Less frequent: respiratory arrest, hypoxia, pulmonary congestion, pleural effusion, asthma, respiratory alkalosis, tachypnoea, wheezing, nasal congestion, hoarseness, rhinitis, hyperventilation, orthopnoea, chest wall pain, sinus pain, throat tightness, productive cough.

Gastrointestinal disorders:

Frequent: vomiting, diarrhoea, nausea, constipation, abdominal pain, stomatitis, dyspepsia, loose stools, abdominal pain upper, flatulence, abdominal distension, hiccups, mouth ulceration, pharyngolaryngeal pain, dry mouth.

Less frequent: acute pancreatitis, paralytic ileus, antibiotic associated colitis, colitis, haematemesis, haemorrhagic diarrhoea, gastrointestinal haemorrhage, rectal haemorrhage, enteritis, dysphagia, abdominal discomfort, eructation, gastrointestinal motility disorder, oral pain, retching, change in bowel habit, spleen pain, oesophagitis, gastritis, gastro-oesophageal reflux disease, gastrointestinal pain, gingival bleeding, gingival pain, hiatus hernia, irritable bowel syndrome, oral mucosal petechiae, salivary hypersecretion, tongue coated, tongue discolouration, faecal impaction.

Hepato-biliary disorder:

Less frequent: hepatitis, hepatic haemorrhage, hypoproteinaemia, hyperbilirubinaemia, hepatotoxicity, acute liver failure (see **section 4.4**).

Skin and subcutaneous tissue disorders:

Frequent: rash, periorbital oedema, urticaria, pruritic rash, pruritus, erythema, increased sweating, dry skin, eczema.

Less frequent: vasculitis rash (including leukocytoclastic vasculitis), erythematous rash, photosensitivity reaction, contusion, generalised pruritus, macular rash, popular rash, psoriasis, generalized rash, eyelid oedema, face oedema, dermatitis, alopecia, nail disorder, skin discolouration, atopic dermatitis, abnormal hair texture, heat rash, night sweats, pressure sore, ichthyosis, skin nodule.

Musculoskeletal and connective tissue disorders:

Frequent: myalgia, muscle weakness, musculoskeletal pain, pain in limb, muscle cramps, arthralgia, bone pain, back pain, peripheral swelling.

Less frequent: muscle spasms, muscle twitching or sensation of heaviness, muscle stiffness, joint swelling, joint stiffness, buttock pain, swelling, pain in jaw.

Renal and urinary disorders:

Frequent: renal impairment, dysuria, acute renal failure, renal failure, oliguria, renal colic, haematuria, proteinuria, urinary retention, urinary frequency, difficulty in micturition, loin pain, urinary incontinence, micturition urgency.

Reproductive system and breast disorders:

Less frequent: testicular pain, erectile dysfunction.

General disorders and administration site disorders:

Frequent: fatigue, pyrexia, asthenia, weakness, lethargy, rigors, malaise, influenza like illness, oedema peripheral, chest pain, pain, oedema.

Less frequent: fall, mucosal haemorrhage, mucosal inflammation, neuralgia, injection site phlebitis, extravasation inflammation tenderness, injection site erythema, feeling cold, chest pressure sensation, chest discomfort, groin pain, chest tightness.

Investigations:

Frequent: decreased weight, increased blood lactate dehydrogenase.

Less frequent: increased alanine aminotransferase, increased aspartate aminotransferase, increased blood bilirubin, increased blood alkaline phosphate, increased blood creatinine, increased blood urea, increased gamma-glutamyltransferase, increased blood amylase, abnormal liver function test, decreased red blood cell count, decreased white blood cell count, decreased blood bicarbonate, irregular heart rate, decreased C-reactive protein, decreased blood phosphate, increased weight.

Injury, poisoning and procedural complications:

Less frequent: catheter related complications, post procedural pain, post procedural haemorrhage, burns.

c) Description of selected adverse reactions

Herpes zoster virus reactivation

Multiple Myeloma

Antiviral prophylaxis was administered to 26 % of the patients in the Vc+M+P arm. The incidence of herpes zoster among patients in the Vc+M+P treatment group was 17 % for patients not administered antiviral prophylaxis compared to 3 % for patients administered antiviral prophylaxis.

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 4.4**).

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-**ONBORT** treatment group (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP) and 0,4 % (n=1) of patients receiving **ONBORT** 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).

Peripheral neuropathy in combination regimens

Multiple Myeloma

In trials in which **ONBORT** was administered as induction treatment in combination with dexamethasone (study IFM-2005-01), and dexamethasone-thalidomide (study MMY-3010), the incidence of peripheral neuropathy in the combination regimens is presented in the table below:

Table 7: Incidence of peripheral neuropathy during induction treatment by toxicity and treatment discontinuation due to peripheral neuropathy

	IFM-2005-01		**MMY-3010**	
	VDDx (N=239)	**VcDx (N=239)**	**TDx (N=126)**	**VcTDx (N=130)**

Incidence of PN (%)				
All GradePN	3	15	12	45
≥ Grade 2 PN	1	10	2	31
≥ Grade 3 PN	< 1	5	0	5
Discontinuation due to PN (%)	< 1	2	1	5

VDDx=vincristine, doxorubicin, dexamethasone; VcDx=**ONBORT**, dexamethasone; TDx=thalidomide, dexamethasone; VcTDx=**ONBORT**, thalidomide, dexamethasone; PN=peripheral neuropathy

Note: Peripheral neuropathy included the preferred terms: neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy.

Mantle cell lymphoma

In study LYM-3002 in which **ONBORT** 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 8: 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 GradePN	30	29
≥ Grade 2 PN	18	9
≥ Grade 3 PN	8	4
Discontinuation due to PN (%)	2	< 1

VcR-CAP=**ONBORT**, 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.

Notable differences in the safety profile of ONBORT administered subcutaneously versus intravenously as single agent

In the Phase III study patients who received **ONBORT** subcutaneously compared to intravenous administration had 13 % lower overall incidence of treatment emergent adverse reactions that were Grade 3 or higher in toxicity, and a 5 % lower incidence of discontinuation of **ONBORT**. The overall incidence of diarrhoea, gastrointestinal and abdominal pain, asthenic conditions, upper respiratory tract infections and peripheral neuropathies were 12 %-15 % lower in the subcutaneous group than in the intravenous group. In addition, the incidence of Grade 3 or higher peripheral neuropathies was 10 % lower, and the discontinuation rate due to peripheral neuropathies 8 % lower for the subcutaneous group as compared to the intravenous group.

Six percent of patients had an adverse local reaction to subcutaneous administration, mostly redness. Cases resolved in a median of 6 days, dose modification was required in two patients. Two (1 %) of the patients had severe reactions; 1 case of pruritus and 1 case of redness.

The incidence of death on treatment was 5 % in the subcutaneous treatment group and 7 % in the intravenous treatment group. Incidence of death from "Progressive disease was 18 % in the subcutaneous group and 9 % in the intravenous group.

Retreatment of patients with relapsed multiple myeloma

In a study in which **ONBORT** retreatment was administered in 130 patients with relapsed multiple myeloma, who previously had at least partial response on a **ONBORT**-containing regimen, the most common all-grade adverse events occurring in at least 25 % of patients were thrombocytopenia (55 %), neuropathy (40 %), anaemia (37 %), diarrhoea (35 %), and constipation (28 %). All grade peripheral neuropathy and grade ≥ 3 peripheral neuropathy were observed in 40 % and 8,5 % of patients, respectively.

d) Paediatric population

ONBORT has not been studied in children and adolescents. Therefore, it should not be used in the paediatric age group until further data become available (see **section 4.2**).

e) Other special population

Elderly patients

There is no evidence to suggest that dose adjustments are necessary in the elderly (see **section 4.8**).

Gender and race

The effects of gender and race on bortezomib have not been evaluated.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/publications/Index/8 or to the Holder of certificate of registration through the mail: pvg.cdma@heterogroups.com.

Post marketing experience

Not Applicable

4.9 Overdose

Overdosage (more than twice the recommended dose) in the setting of concurrent sepsis has been reported. Overdosage is associated with acute onset of the symptomatic hypotension. It is recommended that in the events of overdosage, patients should undergo careful haemodynamic monitoring and hypotension should be treated aggressively with intravenous hydration and other clinically appropriate measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 26 Cytostatic agents

Bortezomib is a selective proteasome inhibitor. It specifically inhibits the chymotrypsin-like activity of the 26S proteasome in mammalian cells.

Mechanism of action

Bortezomib mediated proteasome inhibition affects cells in a number of ways, including, but not limited to, altering regulatory protein, which control cell cycle progression and Nuclear Factor kappa B (NF-kB) activation. Inhibition of the proteasome results in cell cycle arrest and apoptosis. NF-kB is a transcription factor whose activation is required for many aspects of tumorigenesis, including cell growth and survival, angiogenesis, cell:cell interactions, and metastasis. In myeloma, bortezomib affects the ability of myeloma cells to interact with the bone marrow microenvironment.

Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types and that cancer cells are more sensitive to the proapoptotic effects of proteasome inhibition than normal cells. Bortezomib causes reduction of tumour growth *in vivo* in many preclinical tumour models, including multiple myeloma.

5.2 Pharmacokinetic properties

Absorption

Following intravenous bolus administration of a 1,0 mg/m^2 and 1,3 mg/m^2 dose to eleven patients with multiple myeloma, the mean maximum plasma concentrations of bortezomib were 57 and 112 mg/mℓ respectively after the first dose. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/mℓ for the 1,0 mg/m^2 dose and 89 to 120 ng/mℓ for the 1,3 mg/m^2 dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40-193 hours.

Bortezomib is eliminated more rapidly following the first dose compared to subsequent doses. Mean total body clearances were 102 and 112 ℓ/h following the first dose for doses of 1,0 mg/m^2 and 1,3 mg/m^2, respectively, and ranged from 15 to 32 ℓ/h following subsequent doses for doses of 1,0 mg/m^2 and 1,3 mg/m^2, respectively.

Distribution

The mean distribution volume of bortezomib was variable and ranged from 1 659 litres to 3 294 litres following

single- or repeat-dose administration of 1,0 mg/m^2 or 1,3 mg/m^2 to patients with multiple myeloma. This suggests that bortezomib distributes widely to peripheral tissues. The binding of bortezomib to human plasma averaged 83 % over the concentration range 100-1000 mg/ml.

Biotranformation

In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolised via cytochrome P450 enzymes, 3A4, 2C19, and 1A2. Bortezomib metabolism by CYP 206 and 2C9 enzymes is minor. The major metabolic pathway is deboronation to form two 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.

Elimination

The pathways of elimination of bortezomib have not been characterised in humans.

Special populations

Age, Gender and Race

The pharmacokinetics of bortezomib were characterised following twice weekly intravenous bolus administration of 1,3 mg/m^2 doses to 104 paediatric patients (2 - 16 years old) with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML). Based on a population pharmacokinetic analysis, clearance of bortezomib increased with increasing body surface area (BSA). Geometric mean (% CV) clearance was 7,79 (25 %) L/hr/m^2, volume of distribution at steady-state was 834 (39 %) L/m^2, and the elimination half-life was 100 (44 %) hours. After correcting for the BSA effect, other demographics such as age, body weight and sex did not have clinically significant effects on bortezomib clearance. BSA-normalised clearance of bortezomib in paediatric patients was similar to that observed in adults.

The effects of gender and race on the pharmacokinetics of bortezomib have not been evaluated.

Hepatic impairment

The effect of hepatic impairment on the pharmacokinetics of bortezomib was assessed in 51 cancer patients at bortezomib doses ranging from 0,5 to 1,3 mg/m^2. When compared to patients with normal hepatic function, mild hepatic impairment did not alter dose-normalized bortezomib AUC. However, the dose-normalized mean AUC values were increased by approximately 60 % in patients with moderate or severe hepatic impairment. A lower starting dose is recommended in patients with moderate or severe hepatic impairment, and those patients should be monitored closely (see **table 2**).

Renal impairment

A pharmacokinetic study was conducted in patients with various degrees of renal impairment who were classified according to their creatinine clearance values (CrCL) into the following groups: Normal (CrCL ≥ 60 mℓ / min/1,73 m^2, n=12), Mild (CrCL=40-59 mℓ / min/1,73 m^2, n=10), Moderate (CrCL=20-39 mℓ / min/1,73 m^2, n=9), and Severe (CrCL < 20 mℓ / min/1,73 m^2, n=3). A group of dialysis patients who were dosed after dialysis was also included in the study (n=8). Patients were administered intravenous doses of 0,7 to 1,3 mg/m^2 of bortezomib twice weekly. Exposure of bortezomib (dose-normalized AUC and C_{max}) was comparable among all the groups (see **section 4.2**).

5.3 Preclinical safety data

Not Applicable

Environmental Risk Assessment:

Bortezomib is a well established active ingredient used in pharmaceutical preparations for human use. Given the anticipated pattern of use and disposal of the product, the environmental exposure of the active substance and metabolites is expected to be very limited. The use of **ONBORT** is not considered warranting any environmental concerns or requiring any special product labelling.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (3,5 mg/ml)

Nitrogen

Tertiary butyl alcohol

Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C, in a dry place, well closed in original vial, protected from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

Keep the vial in the outer carton.

Reconstituted solution

The reconstituted solution is free from visible particles. May be stored for 8 hours at 25 °C in the original vial and/or in a syringe, prior to administration, with a maximum of 8 hours in the syringe.

NOTE: The injection is for single use only. Discard unused portion after dosing.

6.5 Nature and contents of container

ONBORT is supplied as a single use 10 ml clear, colourless glass vial with a grey bromo-butyl rubber stopper and a rust coloured flip off seal cap. The 10 ml vial contains white to off white cake or powder containing 3,5 mg of bortezomib.

Each vial placed into an outer carton box together with a package insert.

6.6 Special precautions for disposal and other handling

ONBORT IS FOR SINGLE USE ONLY.

ONBORT is a cytotoxic medicine. Therefore, caution should be used during handling and preparation. Use of gloves and other protective clothing to prevent skin contact is recommended.

ASEPTIC TECHNIQUE MUST BE STRICTLY OBSERVED THROUGHOUT HANDLING OF ONBORT SINCE NO PRESERVATIVE IS PRESENT

7 HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9, Parc du Cap

Mispel Street, Bellville

7530

8 REGISTRATION NUMBER(S)

51/26/0053

9 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

March 2020