PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

ZYMIB 3,5 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 3,5 mg bortezomib.

For SC use: After reconstitution, 1 mL of solution for subcutaneous injection contains 2,5 mg bortezomib.

For IV use: After reconstitution, 1 mL of solution for intravenous injection contains 1 mg bortezomib.

Excipients with known effects

Contains sugar: mannitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

A white to off-white colour, lyophilised powder or cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZYMIB is indicated as:

- 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

Posology

ZYMIB 3,5 mg 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 of 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.

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

Monotherapy

Recommended dosage

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

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

Recommended dosage adjustments during treatment and reinitiation of treatment

ZYMIB 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, ZYMIB treatment may be reinitiated 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 ZYMIB must be considered.

Patients who experience ZYMIB-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 ZYMIB only after careful risk/benefit assessment.

Table 1: Recommended* dose modifications for ZYMIB-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 reflexes) 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 ZYMIB treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate ZYMIB 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 ZYMIB.

*Based on dose modifications in phase II and III multiple myeloma studies.

Special populations

Paediatric patients

ZYMIB 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.

Patients with renal impairment

The pharmacokinetics of ZYMIB are not influenced by the degree of renal impairment. Therefore, dosing adjustments of ZYMIB are not necessary for patients with renal insufficiency. Since dialysis may reduce ZYMIB concentrations, ZYMIB 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 ZYMIB dose. Patients with moderate or severe hepatic impairment should be started on ZYMIB at a reduced dose of 0,7 mg/m² 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 ZYMIB 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 ZYMIB 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
Severe	> 3 x ULN	Any	

			based on patient tolerability.

* Based on NCI organ dysfunction working group classification for categorising hepatic impairment (mild, moderate, severe).

** SGOT = serum glutamic oxaloacetic transaminase

*** AST = aspartate aminotransferase

**** ULN = upper limit of the normal range.

Combination therapy

Recommended dosage

ZYMIB 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, ZYMIB is administered twice weekly (Day 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5 – 9, ZYMIB is administered once weekly (Day 1, 8, 22 and 29).

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

Twice weekly ZYMIB (Cycles 1 – 4)						
Week	**1**	**2**	**3**	**4**	**5**	**6**
ZYMIB (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 ZYMIB (Cycles 5 – 9)						
Week	**1**	**2**	**3**	**4**	**5**	**6**
ZYMIB (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

m = melphalan, p = prednisone

Dose management guidelines for combination therapy

Dose modification and reinitiation of therapy when ZYMIB 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 x 10^9/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, 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 × 10^9/L or ANC ≤ 0,75 x 10^9/L on a ZYMIB dosing day (other than Day 1)	ZYMIB dose should be withheld.
• If several ZYMIB doses in a cycle are withheld	ZYMIB dose should be reduced by 1

(≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration)	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	ZYMIB therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, ZYMIB 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 ZYMIB-related neuropathic pain and/or peripheral neuropathy, hold and/or modify ZYMIB as outlined in Table 1.

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

Method of administration

Administration precautions

There have been fatal cases of inadvertent intrathecal administration of ZYMIB.

DO NOT ADMINISTER ZYMIB INTRATHECALLY.

See section 6.6 for reconstitution instructions.

Intravenous (IV) 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 0,9 % sodium chloride solution for injection.

At least 72 hours should elapse between consecutive doses of ZYMIB.

Subcutaneous injection

The reconstituted solution is injected 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 ZYMIB injection subcutaneously, a less concentrated ZYMIB solution (1 mg/mL instead of 2,5 mg/mL) may be administered subcutaneously or changed to IV injection.

4.3 Contraindications

- Hypersensitivity to bortezomib, boron or to any of the excipients listed in section 6.1.
- Acute diffuse infiltrative pulmonary and pericardial disease.

4.4 Special warnings and precautions for use

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

Intrathecal administration

There have been fatal cases of inadvertent intrathecal administration of ZYMIB. ZYMIB is for intravenous or subcutaneous use. **DO NOT ADMINISTER INTRATHECALLY.**

Herpes zoster virus reactivation

Medical practitioners should reconsider using antiviral prophylaxis in patients being treated with ZYMIB.

In studies in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was very common in patients treated with bortezomib + melphalan + prednisone (VcMP) compared with melphalan + prednisone.

Hepatitis B virus (HBV) reactivation and infection

When rituximab is used in combination with ZYMIB, 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 ZYMIB. Antiviral prophylaxis should be considered.

Progressive multifocal leukoencephalopathy (PML)

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

Patients with mantle cell lymphoma

Safety data for patients with mantle cell lymphoma were similar to that observed in patients with multiple myeloma. Notable differences between the two patient populations were that thrombocytopenia, neutropenia, 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 patients with relapsed and/or refractory multiple myeloma, the following special precautions are suggested: Overall, the safety profile of patients treated with bortezomib in monotherapy was similar to that observed in patients treated with

bortezomib in combination with melphalan and prednisone.

Laboratory tests

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

Gastrointestinal toxicity

Gastrointestinal toxicity, including nausea, diarrhoea, vomiting and constipation occur very frequently with ZYMIB 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 antemetics and anti-diarrhoeals. Fluid and electrolyte replacement should be administered to prevent or treat dehydration. Cases of ileus have been reported and therefore patients who experience constipation should be closely monitored.

Haematological toxicity

ZYMIB treatment is frequently associated with haematological toxicities (thrombocytopenia and neutropenia). However, febrile neutropenia is a less frequent undesirable effect. The most frequent haematologic toxicity is transient thrombocytopenia, which generally resolves between treatment cycles. Platelets were lowest at Day 11 of each cycle of ZYMIB 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 central nervous system (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.

Platelet counts should be monitored prior to each dose of ZYMIB. 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). 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.

Peripheral neuropathy

ZYMIB 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 are likely to experience worsening peripheral neuropathy (including ≥ Grade 3) during treatment with ZYMIB. 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, hypaesthesia, paraesthesia, discomfort or neuropathic pain.

Patients experiencing new or worsening peripheral neuropathy may require a change in the dose schedule of ZYMIB (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 medicine 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.

Seizures

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

Hypotension

ZYMIB treatment is frequently associated with orthostatic/postural hypotension. Most patients required treatment for their orthostatic hypotension. Patients with orthostatic hypotension may experience syncopal events. The mechanism of this event is unknown although a component may be due to autonomic neuropathy. Autonomic neuropathy may be related to ZYMIB or ZYMIB may aggravate an underlying condition such as diabetic neuropathy. Caution is advised when treating patients with a history of syncope receiving medicines 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 medicines, 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 studies; causality has not been established.

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

Pulmonary disorders

There have been reports of acute diffuse infiltrative pulmonary disease of unknown aetiology, such as pneumonitis, interstitial pneumonia, lung infiltration and acute respiratory distress syndrome (ARDS) in patients receiving bortezomib (ZYMIB). 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.

In a clinical trial, the first two patients given high-dose cytarabine (2 g/m^2 per day) by continuous infusion in combination with daunorubicin and bortezomib (ZYMIB) for relapsed acute myelogenous leukaemia died of ARDS early in the course of therapy. The trial was discontinued subsequently.

Renal events

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

Hepatic events

Cases of hepatic failure have been reported. Other reported hepatic events include asymptomatic increases in liver enzymes, hyperbilirubinaemia and hepatitis. Such changes may be reversible upon discontinuation of ZYMIB. There is limited rechallenge information in these patients.

Hepatic impairment

Bortezomib is metabolised by liver enzymes (see section 5.2). Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; these patients should be treated with ZYMIB at reduced doses and closely monitored for toxicities (see section 4.2).

Tumour lysis syndrome

Because ZYMIB is a cytotoxic medicine 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, dysrhythmias and syncope. These patients should be monitored closely and appropriate precautions taken.

Amyloidosis

The impact of proteasome inhibition by ZYMIB 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 less frequently. ZYMIB should be discontinued if serious reactions occur.

Reversible posterior leukoencephalopathy syndrome (RPLS)

There have been reports of RPLS in patients receiving ZYMIB. 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 magnetic resonance imaging (MRI), is used to confirm the diagnosis. In patients developing RPLS, ZYMIB should be discontinued.

4.5 Interaction with other medicines and other forms of interaction

In vitro studies indicate that bortezomib 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 bortezomib, the CYP2D6 poor metaboliser phenotype is not expected to affect the

overall disposition of bortezomib.

An interaction study assessing the effect of ketoconazole, a potent CYP3A4 inhibitor, on the pharmacokinetics of bortezomib (injected intravenously), showed a mean bortezomib AUC increase. Therefore, patients should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir).

In an interaction study assessing the effect of omeprazole, a potent CYP2C19 inhibitor, on the pharmacokinetics of bortezomib (injected intravenously), there was no significant effect on the pharmacokinetics of bortezomib.

An interaction study assessing the effect of rifampicin, a potent CYP3A4 inducer, on the pharmacokinetics of bortezomib (injected intravenously), showed a mean bortezomib AUC reduction. Therefore, the concomitant use of bortezomib with strong CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital and St John's wort) is not recommended, as efficacy may be reduced.
In the same interaction study assessing the effect of dexamethasone, a weaker CYP3A4 inducer, on the pharmacokinetics of bortezomib (injected intravenously), there was no significant effect on the pharmacokinetics of bortezomib.

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

An interaction study assessing the effect of melphalan-prednisone on the pharmacokinetics of bortezomib (injected intravenously), showed a mean bortezomib AUC increase. This is not considered clinically relevant.

During clinical trials, hypoglycaemia and hyperglycaemia were uncommonly and commonly

reported in diabetic patients receiving oral hypoglycaemic medicines. Patients on oral antidiabetic medicines receiving ZYMIB may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetic medicines.

4.6 Fertility, pregnancy and lactation

Contraception in males and females

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

Pregnancy

Safety in pregnancy has not been established. The teratogenic potential of bortezomib has not been fully investigated.

If ZYMIB is used during pregnancy, or if the patient becomes pregnant while receiving ZYMIB, the patient needs to be informed of potential for hazards to the fetus.

Breastfeeding

Safety in lactation has not been established.

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

Fertility

Fertility studies have not been conducted.

4.7 Effects on ability to drive and use machines

ZYMIB may have a moderate influence on the ability to drive a vehicle and use machines. ZYMIB may cause side effects, such as fatigue, dizziness, syncope, orthostatic/postural hypotension or blurred vision. Caution is advised before driving a vehicle or operating machinery until the effects

of ZYMIB are known.

4.8 Undesirable effects

Summary of the safety profile

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

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

Tabulated summary of adverse reactions

System organ class	Incidence	Adverse reaction
Infections and infestations	Frequent	herpes zoster (including disseminated and ophthalmic), pneumonia*, herpes simplex*, fungal infection*
	Less frequent	infection*, bacterial infections*, viral infections*, sepsis (including septic shock)*, bronchopneumonia, herpes virus infection*, meningoencephalitis herpetic#, bacteraemia (including staphylococcal), hordeolum, influenza, cellulitis, device-related infection, skin infection*, ear infection*, staphylococcal infection, tooth infection*, meningitis (including bacterial), Epstein-Barr virus infection, genital herpes, tonsillitis, mastoiditis, post-viral fatigue syndrome, upper and lower respiratory tract infection, catheter-related infection, pleural

		infection, *Haemophilus* infection, cytomegalovirus infection, infectious mononucleosis, varicella, urinary tract infection, gastroenteritis, *Candida* infection, fungal infection, post-herpetic neuralgia, oral candidiasis, blepharitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Less frequent	neoplasm malignant, leukaemia plasmacytic, renal cell carcinoma, mass, mycosis fungoides, neoplasm benign*
Blood and lymphatic system disorders	Frequent	thrombocytopenia*, neutropenia*, anaemia*, leukopenia*, lymphopenia*
	Less frequent	pancytopenia*, febrile neutropenia, coagulopathy*, leucocytosis*, lymphadenopathy, haemolytic anaemia#, disseminated intravascular coagulation, thrombocytosis*, hyperviscosity syndrome, platelet disorder NOS, thrombotic microangiopathy (including thrombocytopenic purpura)#, blood disorder NOS, haemorrhagic diathesis, lymphocytic infiltration
Immune system disorders	Less frequent	angioedema#, hypersensitivity*, polyarthritis with rash and proliferative glomerulonephritis, anaphylactic shock, amyloidosis, type III immune complex-mediated reaction, potentially immunocomplex-mediated reactions, such as serum sickness-type reaction
Endocrine disorders	Less frequent	Cushing's syndrome*, hyperthyroidism*, inappropriate antidiuretic hormone secretion, hypothyroidism
Metabolism and nutrition disorders	Frequent	decreased appetite, dehydration, hypokalaemia*, hyponatraemia*, abnormal blood glucose*,

		hypocalcaemia*, enzyme abnormality*
	Less frequent	tumour lysis syndrome (see section 4.4), failure to thrive*, hypomagnesaemia*, hypophosphataemia*, hyperkalaemia*, hypercalcaemia*, hypernatraemia*, abnormal uric acid*, diabetes mellitus*, fluid retention, hypermagnesaemia*, acidosis, electrolyte imbalance*, fluid overload, hypochloraemia*, hypovolaemia, hyperchloraemia*, hyperphosphataemia*, metabolic disorder, vitamin B complex deficiency, vitamin B12 deficiency, gout, increased appetite, alcohol intolerance
Psychiatric disorders	Frequent	mood disorders and disturbances*, anxiety disorder*, sleep disorders and disturbances*, mental disorder*, psychotic disorder*, confusion*
	Less frequent	suicidal ideation*, adjustment disorder, delirium, decreased libido, restlessness, hallucinations
Nervous system disorders	Frequent	neuropathies*, peripheral sensory neuropathy, dysaesthesia*, neuralgia*, motor neuropathy*, loss of consciousness (including syncope), dizziness*, dysgeusia*, lethargy, headache*, tremor
	Less frequent	peripheral sensorimotor neuropathy, dyskinesia*, cerebellar coordination and balance disturbances*, memory loss (excluding dementia)*, encephalopathy*, posterior reversible encephalopathy syndrome#, neurotoxicity, seizure disorders*, post-herpetic neuralgia, speech disorder*, restless legs syndrome, migraine, sciatica, disturbance in attention, abnormal reflexes*, parosmia, cerebral haemorrhage*,

		haemorrhage intracranial (including subarachnoid)*, brain oedema, transient ischaemic attack, coma, autonomic nervous system imbalance, autonomic neuropathy, cranial palsy*, paralysis*, paresis*, presyncope, brain stem syndrome, cerebrovascular disorder, nerve root lesion, psychomotor hyperactivity, spinal cord compression, cognitive disorder NOS, motor dysfunction, nervous system disorder NOS, radiculitis, drooling, hypotonia
Eye disorders	Frequent	eye swelling*, abnormal vision*, conjunctivitis*
	Less frequent	eye haemorrhage*, eyelid infection*, chalazion#, blepharitis#, eye inflammation*, diplopia, dry eye*, eye irritation*, eye pain, lacrimation increased, eye discharge, corneal lesion*, exophthalmos, retinitis, scotoma, eye disorder (including eyelid) NOS, dacryoadenitis acquired, photophobia, photopsia, optic neuropathy#, different degrees of visual impairment (up to blindness)*
Ear and labyrinth disorders	Frequent	vertigo*
	Less frequent	dysacusis (including tinnitus)*, hearing impaired (up to and including deafness), ear discomfort*, ear haemorrhage, vestibular neuronitis, ear disorder NOS
Cardiac disorders	Less frequent	cardiac tamponade#, cardio-pulmonary arrest*, cardiac fibrillation (including atrial), cardiac failure (including left and right ventricular)*, dysrhythmia*, tachycardia*, palpitations, angina pectoris, pericarditis (including pericardial effusion)*, cardiomyopathy*, ventricular

		dysfunction*, bradycardia, atrial flutter, myocardial infarction*, atrioventricular block*, cardiovascular disorder (including cardiogenic shock), torsades de pointes, unstable angina, cardiac valve disorders*, coronary artery insufficiency, sinus arrest, new onset of decreased left ventricular ejection fraction
Vascular disorders	Frequent	hypotension*, orthostatic hypotension, hypertension*, haematoma (including perirenal)*, phlebitis
	Less frequent	cerebrovascular incident#, deep vein thrombosis*, haemorrhage*, thrombophlebitis (including superficial), circulatory collapse (including hypovolaemic shock), flushing*, poor peripheral circulation*, vasculitis, hyperaemia (including ocular)*, peripheral embolism, lymphoedema, pallor, erythromelalgia, vasodilatation, vein discolouration, venous insufficiency
Respiratory, thoracic and mediastinal disorders	Frequent	dyspnoea*, epistaxis, upper/lower respiratory tract infection*, cough*
	Less frequent	pulmonary embolism, pleural effusion, pulmonary oedema (including acute), pulmonary alveolar haemorrhage#, bronchospasm, chronic obstructive pulmonary disease*, hypoxaemia*, respiratory tract congestion*, hypoxia, pleurisy*, hiccups, rhinorrhoea, dysphonia, wheezing, respiratory failure, acute respiratory distress syndrome, apnoea, pneumothorax, atelectasis, pulmonary hypertension, haemoptysis, hyperventilation, orthopnoea, pneumonitis, respiratory alkalosis, tachypnoea, pulmonary fibrosis, bronchial

		disorder*, hypocapnia*, interstitial lung disease, lung infiltration, throat tightness, dry throat, increased upper airway secretion, throat irritation, upper airway cough syndrome
Gastrointestinal disorders	Frequent	nausea and vomiting symptoms*, diarrhoea*, constipation, gastrointestinal haemorrhage (including mucosal)*, dyspepsia, stomatitis*, abdominal distension, oropharyngeal pain*, abdominal pain (including gastrointestinal and splenic pain)*, oral disorder*, flatulence, loose stools, oral ulceration
	Less frequent	pancreatitis (including chronic)*, haematemesis, lip swelling*, gastrointestinal obstruction (including small intestinal obstruction, ileus)*, abdominal discomfort, enteritis*, gastritis*, gingival bleeding, gastroesophageal reflux disease*, colitis (including *Clostridium difficile*)*, colitis ischaemic#, gastrointestinal inflammation*, dysphagia, irritable bowel syndrome, gastrointestinal disorder NOS, tongue coated, gastrointestinal motility disorder*, salivary gland disorder*, pancreatitis acute, peritonitis*, tongue oedema*, ascites, oesophagitis, cheilitis, faecal incontinence, anal sphincter atony, faecaloma*, gastrointestinal ulceration and perforation*, gingival hypertrophy, megacolon, rectal discharge, oropharyngeal blistering*, lip pain, periodontitis, anal fissure, change of bowel habit, proctalgia, abnormal faeces
Hepatobiliary	Frequent	hepatic enzyme abnormality*

disorders	Less frequent	hepatotoxicity (including liver disorder), hepatitis*, cholestasis, hepatic failure, hepatomegaly, Budd-Chiari syndrome, cytomegalovirus hepatitis, hepatic haemorrhage, cholelithiasis, hypoproteinaemia, hyperbilirubinaemia
Skin and subcutaneous tissue disorders	Frequent	rash*, pruritus*, erythema, dry skin, periorbital oedema, eczema, increased sweating
	Less frequent	erythema multiforme, urticaria, acute febrile neutrophilic dermatosis, toxic skin eruption, toxic epidermal necrolysis#, Stevens-Johnson syndrome#, dermatitis*, hair disorder*, petechiae, ecchymosis, skin lesion, purpura, skin mass*, psoriasis, hyperhidrosis, night sweats, decubitus ulcer#, acne*, blister*, pigmentation disorder*, skin reaction, Jessner's lymphocytic infiltration, palmar-plantar erythrodysaesthesia syndrome, haemorrhage subcutaneous, livedo reticularis, skin induration, papule, photosensitivity reaction, seborrhoea, cold sweat, skin disorder NOS, erythrosis, skin ulcer, nail disorder
Musculoskeletal and connective tissue disorders	Frequent	musculoskeletal pain*, muscle spasms*, pain in extremity, muscular weakness, bone pain, peripheral swelling, muscle cramps, myalgia, back pain
	Less frequent	muscle twitching, joint swelling, arthritis*, joint stiffness, myopathies*, sensation of heaviness, rhabdomyolysis, temporomandibular joint syndrome, fistula, joint effusion, pain in jaw, bone disorder, musculoskeletal and connective tissue infections and inflammations*,

		synovial cyst, buttock pain
Renal and urinary disorders	Frequent	renal impairment*, dysuria
	Less frequent	renal failure acute, renal failure chronic*, urinary tract infection*, urinary tract signs and symptoms*, haematuria*, urinary retention, micturition disorder*, proteinuria, azotaemia, oliguria*, pollakiuria, bladder irritation, renal colic, urinary frequency, loin pain, urinary incontinence
Reproductive system and breast disorders	Less frequent	vaginal haemorrhage, genital pain*, erectile dysfunction, testicular disorder*, prostatitis, breast disorder female, epididymal tenderness, epididymitis, pelvic pain, vulval ulceration
Congenital, familial and genetic disorders	Less frequent	aplasia, gastrointestinal malformation, ichthyosis
General disorders and administration site conditions	Frequent	pyrexia*, fatigue, asthenia, oedema (including peripheral), chills, pain*, malaise*
	Uncommon	general physical health deterioration*, face oedema*, injection site reaction*, mucosal disorder*, chest pain, gait disturbance, feeling cold, extravasation*, catheter-related complication*, change in thirst*, chest discomfort, feeling of body temperature change*, injection site pain*, death (including sudden), multi-organ failure, injection site haemorrhage*, hernia (including hiatus)*, impaired healing*, inflammation, injection site phlebitis*, tenderness, ulcer, irritability, non-cardiac chest pain, catheter site pain, sensation of foreign body

Investigations	Frequent	decreased body mass, blood lactate dehydrogenase increased
	Less frequent	hyperbilirubinaemia*, protein analyses abnormal*, increased body mass, abnormal blood test*, increased C-reactive protein, abnormal blood gases*, electrocardiogram abnormalities (including QT prolongation)*, abnormal international normalised ratio*, decreased gastric pH, increased platelet aggregation, increased troponin I, virus identification and serology*, abnormal urine analysis*, increased blood alkaline phosphatase, increased blood creatinine, increased blood urea, increased gamma glutamyl transferase, increased blood amylase, abnormal liver function tests, decreased red blood cell count, decreased white blood cell count, decreased blood bicarbonate, irregular heart rate, decreased blood phosphate
Injury, poisoning and procedural complications	Less frequent	fall, contusion, transfusion reaction, fractures*, rigors*, face injury, joint injury*, burns, laceration, procedural pain, radiation injuries*
Surgical and medical procedures	Less frequent	macrophage activation

NOS = not otherwise specified.

* Grouping of more than one MedDRA preferred term.

Post-marketing adverse reaction regardless of indication.

Mantle cell lymphoma (MCL)

The safety profile of bortezomib in MCL patients treated with bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (BR-CAP) versus patients treated with

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

Description of selected adverse reactions

Herpes zoster virus reactivation

Antiviral prophylaxis decreases the incidence of herpes zoster.

Mantle cell lymphoma

Antiviral prophylaxis decreases the incidence of herpes zoster.

Hepatitis B virus (HBV) reactivation and infection

Mantle cell lymphoma

HBV infection with fatal outcome was decreased when ZYMIB was given in combination with rituximab, cyclophosphamide, doxorubicin and prednisone.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of ZYMIB is important. It allows continued monitoring of the benefit/risk balance of ZYMIB. Healthcare providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety App (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA's website.

4.9 Overdose

In patients, overdose with more than twice the recommended dose has been associated with the acute onset of symptomatic hypotension and thrombocytopenia, with fatal outcomes. One case of overdosage (more than twice the recommended dose) in the setting of concurrent sepsis has been reported with ZYMIB.

Management

There is no known specific antidote for ZYMIB 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 medicines) and body temperature (see sections 4.2 and 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 26 Cytostatic agents.

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents.

ATC code: L01XX32.

Mechanism of action

Bortezomib is a selective proteasome inhibitor. It specifically inhibits the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the turnover of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis and affects multiple signalling cascades within the cell, ultimately resulting in cancer cell death.

Bortezomib is highly selective for the proteasome. At 10 μM concentrations, bortezomib does not inhibit any of a wide variety of receptors and proteases screened and is more than 1 500-fold more

selective for the proteasome than for its next preferable enzyme. The kinetics of proteasome inhibition were evaluated *in vitro*, and bortezomib was shown to dissociate from the proteasome with a half-life of 20 minutes, thus demonstrating that proteasome inhibition by bortezomib is reversible.

Bortezomib-mediated proteasome inhibition affects cancer cells in a number of ways, including, but not limited to, altering regulatory proteins, 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 tumourogenesis, 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 pro-apoptotic 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 and creatinine clearance values greater than 50 mL/min, the mean first-dose maximum plasma concentrations of bortezomib were 57 ng/mL and 112 ng/mL, respectively. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 ng/mL to 106 ng/mL for the 1,0 mg/m^2 dose and 89 ng/mL to 120 ng/mL for the 1,3 mg/m^2 dose.

Following an intravenous bolus or subcutaneous injection of a 1,3 mg/m^2 dose to patients with multiple myeloma, the total systemic exposure after repeat dose administration (AUC_{last}) was equivalent for subcutaneous and intravenous administrations. The C_{max} after subcutaneous

administration (20,4 ng/mL) was lower than intravenous (223 ng/mL). The AUC_{last} geometric mean ratio was 0,99 and 90 % confidence intervals were 80,18 % – 122,80 %.

Distribution

The mean distribution volume (Vd) of bortezomib ranged from 1 659 L to 3 294 L following single- or repeated-dose intravenous 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. Over a bortezomib concentration range of 0,01 µg/mL to 1,0 µg/mL, the *in vitro* protein binding averaged 82,9 % in human plasma. The fraction of bortezomib bound to plasma proteins was not concentration dependent.

Biotransformation

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. 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 minutes and 30 minutes after dosing indicate that the plasma levels of metabolites are low compared to the parent.

Elimination

The mean elimination half-life ($t_{1/2}$) of bortezomib upon multiple dosing ranged from 40 to 193 hours. Bortezomib is eliminated more rapidly following the first dose compared to subsequent doses. Mean total body clearances were 102 L/h 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 L/h to 32 L/h and 18 L/h to 32 L/h following subsequent doses for doses of 1,0 mg/m^2 and 1,3 mg/m^2, respectively.
The pathway of elimination of bortezomib has not been characterised in humans.

Pharmacokinetics in special populations

Hepatic impairment

The effect of hepatic impairment on the pharmacokinetics of bortezomib was assessed in patients primarily with solid tumours and varying degrees of hepatic impairment at bortezomib doses ranging from 0,5 mg/m^2 to 1,3 mg/m^2.

When compared to patients with normal hepatic function, mild hepatic impairment did not alter dose-normalised bortezomib area under the curve (AUC). However, the dose-normalised 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 closely monitored (see section 4.2).

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), mild (CrCL = 40 – 59 mL/min/1,73 m^2), moderate (CrCL = 20 – 39 mL/min/1,73 m^2), and severe (CrCL < 20 mL/min/1,73 m^2). A group of dialysis patients who were dosed after dialysis was also included in the study. Patients were administered intravenous doses of 0,7 mg/m^2 to 1,3 mg/m^2 of bortezomib twice weekly. Exposure of bortezomib (dose-normalised AUC and C_{max}) was comparable among all the groups (see section 4.2).

Age

The pharmacokinetics of bortezomib were characterised following twice weekly intravenous bolus administration of 1,3 mg/m^2 doses to paediatric patients (2 – 16 years old) with acute lymphoblastic leukaemia (ALL) or acute myeloid leukaemia (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/h/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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol.

6.2 Incompatibilities

ZYMIB must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

2 years.

Reconstituted solution

The reconstituted solution should be used immediately after preparation. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. However, the chemical and physical in-use stability of the reconstituted solution has been demonstrated for 12 hours at 25 °C stored in the original vial and/or a syringe. The total storage time for the reconstituted medicine should not exceed 12 hours prior to administration.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

Keep the vial in the outer carton until required for use.

6.5 Nature and contents of container

10 mL, 13 mm USP Type I clear tubular glass vials with 13 mm RTU, double slotted, grey colour, bromobutyl rubber stopper and 13 mm aluminium seal with black flip-off top. One vial is packed in an outer carton.

6.6 Special precautions for disposal and other handling

General precautions

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

Aseptic technique must be strictly observed throughout the handling of ZYMIB, since it contains no preservative.

There have been fatal cases of inadvertent intrathecal administration of ZYMIB. ZYMIB is for intravenous or subcutaneous use.

ZYMIB should not be administered intrathecally.

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.

Instructions for reconstitution

ZYMIB must be reconstituted by a health care provider.

Intravenous injection

Each 10 mL vial of ZYMIB must be carefully reconstituted with 3,5 mL of sodium chloride 9 mg/mL (0,9 %) solution for injection, by using a syringe of the appropriate size, without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.

After reconstitution, each mL solution contains 1 mg bortezomib. 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 solution must be discarded.

Subcutaneous injection

Each 10 mL vial of ZYMIB must be carefully reconstituted with 1,4 mL of sodium chloride 9 mg/mL (0,9 %) solution for injection, by using a syringe of the appropriate size, without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.
After reconstitution, each mL solution contains 2,5 mg bortezomib. 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 solution must be discarded.

Disposal

ZYMIB is for single use only. Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park

Building B, Ground Floor

22 Karee Street

Centurion, Pretoria

0157

8. REGISTRATION NUMBER

54/26/0834

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

10 September 2024

10. DATE OF REVISION OF THE TEXT

Not applicable.