Borcade®

Bortezomib

FORMS AND PRESENTATION
Borcade®: Lyophilized powder for injection; vials; Box of 1.
COMPOSITION
Borcade®: Each vial contains Bortezomib 3.5 mg.
Excipients: mannitol, tertiary butyl alcohol, water for injection.
PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: L01XX32.
Bortezomib is a proteasome inhibitor. It is specifically designed to inhibit the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the turnover of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis and affects multiple signaling 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 t½ 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 tumourigenesis, 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.
Pharmacokinetic properties
Absorption
Following intravenous bolus administration of a 1.0 mg/m2 and 1.3 mg/m2 dose with multiple myeloma and creatinine clearance values greater than 50 ml/min, the mean first-dose maximum plasma concentrations of Bortezomib were 57 and 112 ng/ml, respectively.
Following an intravenous bolus or subcutaneous injection of a 1.3 mg/m2 dose to patients with multiple myeloma (n=14 in the intravenous group, n=17 in the subcutaneous group), the total systemic exposure after repeat dose administration (AUClast) was equivalent for subcutaneous and intravenous administrations. The Cmax after subcutaneous administration (20.4 ng/ml) was lower than intravenous (223 ng/ml). The AUClast 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/m2 or 1.3 mg/m2 to patients with multiple myeloma. Over a Bortezomib concentration range of 0.01 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 metabolized via cytochrome P450 enzymes, 3A4, 2C19, and 1A2. The major metabolic pathway is deboronation Deboronated-Bortezomib metabolites are inactive as 26S proteasome inhibitors.
Elimination
The mean elimination half-life (t1/2) 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/m2 and 1.3 mg/m2, respectively, and ranged from 15 to 32 l/h and 18 to 32 l/h following subsequent doses for doses of 1.0 mg/m2 and 1.3 mg/m2, respectively.
INDICATIONS
Borcade® as monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone is indicated for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation.
Borcade® in combination with melphalan and prednisone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.
Borcade® in combination with dexamethasone, or with dexamethasone and thalidomide, is indicated for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.
Borcade® in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.
CONTRAINDICATIONS
- Hypersensitivity to the active substance, to boron or to any of the excipients listed.
- Acute diffuse infiltrative pulmonary and pericardial disease.
PRECAUTIONS
Intrathecal administration
Bortezomib 1 mg powder for solution for injection is for intravenous use only, while Bortezomib 3.5 mg powder for solution for injection is for intravenous or subcutaneous use. Bortezomib should not be administered intrathecally.
Gastrointestinal toxicity
Patients who experience constipation should be closely monitored.
Haematological toxicity
Bortezomib treatment is very commonly associated with haematological toxicities (thrombocytopenia, neutropenia and anaemia).
Gastrointestinal and intracerebral haemorrhage, have been reported in association with Bortezomib treatment. Therefore, platelet counts should be monitored prior to each dose of Bortezomib. Bortezomib therapy should be withheld when the platelet count is < 25,000/µl or, in the case of combination with melphalan and prednisone, when the platelet count is ≤ 30,000/µl. Complete blood counts (CBC) with differential and including platelet counts should be frequently monitored throughout treatment with Bortezomib. Platelet transfusion should be considered when clinically appropriate.
In patients with MCL, transient neutropenia that was reversible between cycles was observed. Since patients with neutropenia are at increased risk of infections, they should be monitored for signs and symptoms of infection and treated promptly. Granulocyte colony stimulating factors may be administered for haematologic toxicity according to local standard practice. Prophylactic use of granulocyte colony stimulating factors should be considered in case of repeated delays in cycle administration.
Herpes zoster virus reactivation
Antiviral prophylaxis is recommended in patients being treated with Bortezomib.
In the Phase III study in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was more common in patients treated with Bortezomib +Melphalan+Prednisone compared with Melphalan+Prednisone (14% versus 4% respectively).
In patients with MCL (study LYM-3002), the incidence of herpes zoster infection was 6.7% in the VcR-CAP arm and 1.2% in the R-CHOP arm.
Hepatitis B Virus (HBV) reactivation and infection
When rituximab is used in combination with Bortezomib, HBV screening must always be performed in patients at risk of infection with HBV before initiation of treatment. Antiviral prophylaxis should be considered.
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 Bortezomib. Discontinue Bortezomib if PML is diagnosed.
Peripheral neuropathy
Treatment with Bortezomib is very commonly associated with peripheral neuropathy, which is predominantly sensory. It is recommended that patients be carefully monitored for symptoms of neuropathy such as a burning sensation, hyperesthesia, hypoesthesia, paraesthesia, discomfort, neuropathic pain or weakness.
Early and regular monitoring for symptoms of treatment-emergent neuropathy with neurological evaluation should be considered in patients receiving Bortezomib in combination with medicinal products known to be associated with neuropathy (e.g. thalidomide) and appropriate dose reduction or treatment discontinuation should be considered.
Seizures
Seizures have been uncommonly reported in patients without previous history of seizures or epilepsy.
Hypotension
Bortezomib treatment is commonly associated with orthostatic/postural hypotension.
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 diarrhea or vomiting. Management of orthostatic/postural hypotension 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.
Posterior Reversible Encephalopathy Syndrome (PRES)
PRES is a rare, often reversible, rapidly evolving neurological condition, which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. In patients developing PRES, Bortezomib should be discontinued.
Heart failure
Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported during bortezomib treatment. Fluid retention may be a predisposing factor for signs and symptoms of heart failure.
Pulmonary disorders
There have been rare 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. Some of these events have been fatal. A pre-treatment chest radiograph is recommended to serve as a baseline for potential post-treatment pulmonary changes.
In the event of new or worsening pulmonary symptoms (e.g., cough, dyspnoea), a prompt diagnostic evaluation should be performed and patients treated appropriately. The benefit/risk ratio should be considered prior to continuing Bortezomib therapy.
Renal impairment
Renal complications are frequent in patients with multiple myeloma.
Hepatic impairment
Bortezomib is metabolized by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; these patients should be treated with Bortezomib at reduced doses and closely monitored for toxicities.
Hepatic reactions
Rare cases of hepatic failure have been reported in patients receiving. Other reported hepatic reactions include increases in liver enzymes, hyperbilirubinaemia, and hepatitis.
Tumour lysis syndrome
Because bortezomib is a cytotoxic agent and can rapidly kill malignant plasma cells and MCL 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.
Potentially immunocomplex-mediated reactions
Potentially immunocomplex-mediated reactions, such as serum-sickness-type reaction, polyarthritis with rash and proliferative glomerulonephritis have been reported uncommonly. Bortezomib should be discontinued if serious reactions occur.
Effects on ability to drive and use machines
Bortezomib may be associated with fatigue very commonly, dizziness commonly, syncope uncommonly and orthostatic/postural hypotension or blurred vision commonly. Therefore, patients must be cautious when driving or using machines.
FERTILITY, PREGNANCY AND LACTATION
Contraception in males and females
Male and female patients of childbearing potential must use effective contraceptive measures during and for 3 months following treatment.
Pregnancy
Bortezomib should not be used during pregnancy unless the clinical condition of the woman requires treatment with Bortezomib.
Patients receiving Bortezomib in combination with thalidomide should adhere to the pregnancy prevention programme of thalidomide.
Breast-feeding
Breast-feeding should be discontinued during treatment with Bortezomib.
DRUG INTERACTIONS
- 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.
- Patients should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir).
- In a drug-drug interaction study assessing the effect of omeprazole, here was no significant effect on the pharmacokinetics of bortezomib.
- A drug-drug interaction study assessing the effect of rifampicin, 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 drug-drug interaction study assessing the effect of dexamethasone, there was no significant effect on the pharmacokinetics of bortezomib.
- A drug-drug 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, hypoglycemia and hyperglycemia were uncommonly and commonly reported in diabetic patients receiving oral hypoglycemics. Patients on oral antidiabetic agents receiving Bortezomib treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetics.
ADVERSE EFFECTS
The most commonly reported adverse reactions during treatment with Bortezomib are nausea, diarrhea, constipation, vomiting, fatigue, pyrexia, thrombocytopenia, anaemia, neutropenia, peripheral neuropathy (including sensory), headache, paraesthesia, decreased appetite, dyspnoea, rash, herpes zoster and myalgia.
Adverse reactions in patients with Multiple Myeloma treated with Bortezomib as single agent or in combination:
- Infections and infestations: Herpes zoster (inc disseminated & ophthalmic), Pneumonia, Herpes simplex, Fungal infection (common); Infection, Bacterial infections, Viral infections, Sepsis (inc septic shock), Bronchopneumonia, Herpes virus infection, Meningoencephalitis herpetic, Bacteraemia (inc staphylococcal), Hordeolum, Influenza, Cellulitis, Device related infection, Skin infection, Ear infection, Staphylococcal infection, Tooth infection (uncommon).
- Blood and lymphatic system disorders: Thrombocytopenia, Neutropenia, Anaemia (very common); Leukopenia, Lymphopenia (common); Pancytopenia, Febrile neutropenia, Coagulopathy, Leukocytosis, Lymphadenopathy, Haemolytic anaemia (uncommon).
- Immune system disorders: Angioedema, Hypersensitivity (uncommon).
- Endocrine disorders: Cushing's syndrome, Hyperthyroidism, Inappropriate antidiuretic hormone secretion (uncommon).
- Metabolism and nutrition disorders: Decreased appetite (very common); Dehydration, Hypokalaemia, Hyponatraemia, Blood glucose abnormal, Hypocalcaemia, Enzyme abnormality (common); Tumour lysis syndrome, Failure to thrive, Hypomagnesaemia, Hypophosphataemia, Hyperkalaemia, Hypercalcaemia, Hypernatraemia, Uric acid abnormal, Diabetes mellitus, Fluid retention (uncommon).
- Psychiatric disorders: Mood disorders and disturbances, Anxiety disorder, Sleep disorders and disturbances (common); Mental disorder, Hallucination, Psychotic disorder, Confusion, Restlessness (uncommon).
- Nervous system disorders: Neuropathies, Peripheral sensory neuropathy, Dysaesthesia, Neuralgia (Very Common); Motor neuropathy, Loss of consciousness (inc syncope), Dizziness, Dysgeusia, Lethargy, Headache (common); Tremor, Peripheral sensorimotor neuropathy, Dyskinesia, Cerebellar coordination and balance disturbances, Memory loss (exc dementia), Encephalopathy, Posterior Reversible Encephalopathy Syndrome, Neurotoxicity, Seizure disorders, Post herpetic neuralgia, Speech disorder, Restless legs syndrome, Migraine, Sciatica, Disturbance in attention, Reflexes abnormal, Parosmia (uncommon).
- Eye disorders: Eye swelling, Vision abnormal, Conjunctivitis (common); Eye haemorrhage, Eyelid infection, Eye inflammation, Diplopia, Dry eye, Eye irritation, Eye pain, Lacrimation increased,

Eye discharge (uncommon).
- Ear and labyrinth disorders: Vertigo (common); Dysacusis (inc tinnitus), Hearing impaired (up to and inc deafness), Ear discomfort (uncommon).
- Cardiac disorders: Cardiac tamponade, Cardio-pulmonary arrest, Cardiac fibrillation (inc atrial), Cardiac failure (inc left and right ventricular), Arrhythmia, Tachycardia, Palpitations, Angina pectoris, Pericarditis (inc pericardial effusion), Cardiomyopathy, Ventricular dysfunction, Bradycardia (uncommon).
- Vascular disorders: Hypotension, Orthostatic hypotension, Hypertension (common); Cerebrovascular accident, Deep vein thrombosis, Haemorrhage, Thrombophlebitis (inc superficial), Circulatory collapse (inc hypovolaemic shock), Phlebitis, Flushing, Haematoma (inc perirenal), Poor peripheral circulation, Vasculitis, Hyperaemia (inc ocular) (uncommon).
- Respiratory, thoracic and mediastinal disorders: Dyspnoea, Epistaxis, Upper/lower respiratory tract infection, Cough (common); Pulmonary embolism, Pleural effusion, Pulmonary oedema (inc acute), Pulmonary alveolar haemorrhage, Bronchospasm, Chronic obstructive pulmonary disease, Hypoxaemia, Respiratory tract congestion, Hypoxia, Pleurisy, Hiccups, Rhinorrhoea, Dysphonia, Wheezing (uncommon).
-Gastrointestinal disorders: Nausea and vomiting symptoms, Diarrhoea, Constipation (very common); Gastrointestinal haemorrhage (inc mucosal), Dyspepsia, Stomatitis, Abdominal distension, Oropharyngeal pain, Abdominal pain (inc gastrointestinal and splenic pain), Oral disorder, Flatulence (common); Pancreatitis (inc chronic), Haematemesis, Lip swelling, Gastrointestinal obstruction (inc small intestinal obstruction, ileus), Abdominal discomfort, Oral ulceration, Enteritis, Gastritis, Gingival bleeding, Gastrooesophageal reflux disease, Colitis (inc clostridium difficile), Colitis ischaemic, Gastrointestinal inflammation, Dysphagia, Irritable bowel syndrome, Gastrointestinal disorder NOS, Tongue coated, Gastrointestinal motility disorder, Salivary gland disorder (uncommon).
- Hepatobiliary disorders: Hepatic enzyme abnormality (common); Hepatotoxicity (inc liver disorder), Hepatitis, Cholestasis (uncommon).
- Skin and subcutaneous tissue disorders: Rash, Pruritus, Erythema, Dry skin (common); 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 (uncommon).
- Musculoskeletal and connective tissue disorders: Musculoskeletal pain (very common); Muscle spasms, Pain in extremity, Muscular weakness (common); Muscle twitching, Joint swelling, Arthritis, Joint stiffness, Myopathies, Sensation of heaviness (uncommon).
- Renal and urinary disorders: Renal impairment (common); Renal failure acute, Renal failure chronic, Urinary tract infection, Urinary tract signs and symptoms, Haematuria, Urinary retention, Micturition disorder, Proteinuria, Azotaemia, Oliguria, Pollakiuria (uncommon).
- Reproductive system and breast disorders: Vaginal haemorrhage, Genital pain, Erectile dysfunction (uncommon).
- General disorders and administration site conditions: Pyrexia, Fatigue, Asthenia (very common); Oedema (inc peripheral), Chills, Pain, Malaise (common); 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 (uncommon).
- Investigations: Weight decreased (common); Hyperbilirubinaemia, Protein analyses abnormal, Weight increased, Blood test abnormal, C-reactive protein increased (uncommon).

DOSAGE AND ADMINISTRATION

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

Monotherapy

Borcade® 3.5 mg powder for solution for injection is administered via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11 in a 21-day treatment cycle. This 3-week period is considered a treatment cycle. It is recommended that patients receive 2 cycles of Borcade® following a confirmation of a complete response. It is also recommended that responding patients who do not achieve a complete remission receive a total of 8 cycles of Borcade® therapy. At least 72 hours should elapse between consecutive doses of Borcade®.

Dose adjustments during treatment and re-initiation of treatment for monotherapy

Borcade® treatment must be withheld at the onset of any Grade 3 non-haematological or any Grade 4 haematological toxicities, excluding neuropathy. Once the symptoms of the toxicity have resolved, Borcade® treatment may be re-initiated at a 25% reduced dose (1.3 mg/m^2 reduced to 1.0 mg/m^2; 1.0 mg/m^2 reduced to 0.7 mg/m^2). If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of Borcade® must be considered unless the benefit of treatment clearly outweighs the risk.

Neuropathic pain and/or peripheral neuropathy

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

Table 1: Recommended posology modifications for bortezomib-related neuropathy

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

Combination therapy with pegylated liposomal doxorubicin

Borcade® can be given together with pegylated liposomal doxorubicin, intravenously or subcutaneously as a 21-day treatment cycle and pegylated liposomal doxorubicin 30 mg/m^2 is given on day 4 of the Borcade® 21-day treatment cycle as a 1 hour intravenous infusion after the Borcade® injection. You might receive up to 8 cycles (24 weeks).

Combination with dexamethasone

Borcade® can be given together with dexamethasone, intravenously or subcutaneously as a 21-day treatment cycle and dexamethasone 20 mg is given orally on days 1, 2, 4, 5, 8, 9, 11, and 12, of Borcade®, 21-day treatment cycle. Patients achieving a response or a stable disease after 4 cycles of this combination therapy can continue to receive the same combination for a maximum of 4 additional cycles.

Dose adjustments for combination therapy for patients with progressive multiple myeloma

For Borcade® dosage adjustments for combination therapy follow dose modification guidelines described under monotherapy above.

Posology for previously untreated multiple myeloma patients not eligible for haematopoietic stem cell transplantation

Combination therapy with melphalan and prednisone

Previously untreated patients for multiple myeloma and not suitable for blood stem cell transplantation, will receive Borcade® together with two other medicines; melphalan and prednisone.

In this case, the duration of a treatment cycle is 42 days (6 weeks). They will receive 9 cycles (54 weeks).

• In cycles 1 to 4, Borcade® is administered twice weekly on days 1, 4, 8, 11, 22, 25, 29 and 32.

• In cycles 5 to 9, Borcade® is administered once weekly on days 1, 8, 22 and 29.

Melphalan (9 mg/m^2) and prednisone (60 mg/m^2) are both given orally on days 1, 2, 3 and 4 of the first week of each cycle. Combination therapy with dexamethasone or dexamethasone and thalidomide

Previously untreated patients for multiple myeloma, and suitable for blood stem cell transplantation, will receive Borcade® intravenously or subcutaneously together with the medicines dexamethasone, or dexamethasone and thalidomide, as induction treatment.

• Borcade® is given together with dexamethasone intravenously or subcutaneously as a 21-day treatment cycle and dexamethasone 40 mg is given orally on days 1, 2, 3, 4, 8, 9, 10 and 11 of the Borcade® 21-day treatment cycle. 3-week period is considered a treatment cycle. The patient will receive 4 cycles (12 weeks).

• Borcade® is given together with thalidomide and dexamethasone; the duration of a treatment cycle is 28 days (4 weeks).

Dexamethasone 40 mg is given orally on days 1, 2, 3, 4, 8, 9, 10 and 11 of the Borcade® 28-day treatment cycle and thalidomide is given orally daily at 50 mg up to day 14 of the first cycle, and if tolerated the thalidomide dose is increased to 100 mg on days 15-28 and may be further increased to 200 mg daily from the second cycle onwards. Four treatment cycles of this combination are administered. It is recommended that patients with at least partial response receive 2 additional cycles.

Previously untreated mantle cell lymphoma

Previously untreated patients for mantle cell lymphoma will receive Borcade® intravenously or subcutaneously together with the medicines rituximab, cyclophosphamide, doxorubicin and prednisone. Borcade® is given intravenously or subcutaneously on days 1, 4, 8 and 11, followed by a 'rest period' without treatment. The duration of a treatment cycle is 21 days (3 weeks). Patients might receive up to 8 cycles (24 weeks). The following medicinal products are given on day 1 of each Borcade® 21-day treatment cycle as intravenous infusions: Rituximab at 375 mg/m^2, cyclophosphamide at 750 mg/m^2 and doxorubicin at 50 mg/m^2. Prednisone is given orally at 100 mg/m^2 on days 1, 2, 3, 4 and 5 of the Borcade® treatment cycle.

Special populations

Elderly

There is no evidence to suggest that dose adjustments are necessary in patients over 65 years of age.

Hepatic impairment

Patients with mild hepatic impairment do not require a dose adjustment and should be treated per the recommended dose. Patients with moderate or severe hepatic impairment should be started on Borcade® at a reduced dose of 0.7 mg/m^2 per injection during the first treatment cycle, and a subsequent dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 may be considered based on patient tolerability.

Renal impairment

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

Pediatric population

The safety and efficacy of Borcade® in children below 18 years of age have not been established.

Method of administration

Borcade® 3.5 mg powder for solution for injection is available for intravenous or subcutaneous administration. Borcade® should not be given by other routes. Intrathecal administration has resulted in death.

Intravenous injection

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

Subcutaneous injection

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

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

Instructions for reconstitution

Borcade® must be reconstituted by a healthcare professional.

Intravenous injection

Each vial of Borcade® 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 lyophilized powder is completed in less than 2 minutes.

After reconstitution, each ml solution contains 1 mg bortezomib.

Subcutaneous injection

Each vial of Borcade® 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 lyophilized powder is completed in less than 2 minutes.

After reconstitution, each ml solution contains 2.5 mg bortezomib.

OVERDOSAGE

In patients, overdose more than twice the recommended dose has been associated with the acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes.

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

STORAGE CONDITIONS

Store below 30°C.

Keep in original pack in intact conditions. Protect from light.

Stability of Reconstituted solution

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

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Manufactured by Hetero Labs Limited, India
Packed by Benta S.A.L., Lebanon.

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists