Risk Management Plan Induction Transplant Regimens Graph

Bortezomib SPC®

(Bortezomib 3.5 mg powder for solution for injection)

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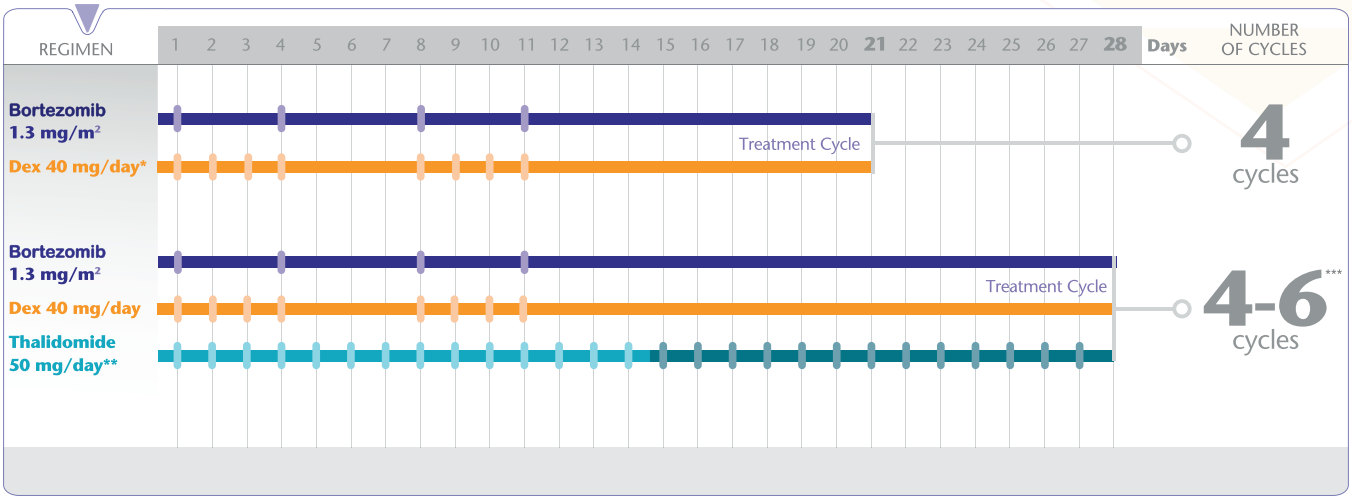
Induction Regimes Prior to Transplant: Dosing and Duration of Treatment



- Dexamethasone is administered orally at 40 mg on days 1, 2, 3, 4 and 8, 9, 10, 11 of the Bortezomib SPC® treatment cycles.
- Thalidomide dose is increased to 100 mg from week 3 of cycle 1 only if 50 mg is tolerated and to 200 mg from cycle 2 onwards if 100 mg is tolerated.
- Patients receiving Bortezomib SPC® in combination with Thalidomide should adhere to the pregnancy prevention programme of Thalidomide. Refer to the Product Information for additional information.
- Up to 6 cycles may be given to patients who achieve at least a partial response after 4 cycles.

Bortezomib SPC® 3.5 mg Powder for Solution for Injection

Prescribing Information

Active Ingredient: Bortezomib

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

Indications: Adults only.

Monotherapy or with pegylated liposomal doxorubicin or dexamethasone: progressive multiple myeloma in patients who have had at least 1 prior therapy and already undergone/are not suitable for haematopoietic stem cell transplant.

With melphalan & prednisone: for previously untreated multiple myeloma in patients not eligible for high-dose chemotherapy with haematopoietic stem cell transplant.

With dexamethasone, or with dexamethasone and thalidomide:

for induction treatment of previously untreated multiple myeloma in patients eligible for high-dose chemotherapy with haematopoietic stem cell transplant.

With rituximab, cyclophosphamide, doxorubicin and prednisone:

for previously untreated mantle cell lymphoma (MCL) in patients unsuitable for haematopoietic stem cell transplantation.

Dosage & Administration:

Adults and Elderly:

Administer as 3-5 second IV bolus or SC in thighs/abdomen. At least 72 hours between consecutive doses.

Recommended dose 1.3mg/m2 body surface area.

Posology modifications required for BORTEZOMIB SPC -related toxicity, refer to SmPC.

Treatment of progressive multiple myeloma (after at least 1 prior therapy) BORTEZOMIB SPC treatment cycle:

twice weekly for 2 weeks in 21-days treatment cycle.

Two cycles of BORTEZOMIB SPC recommended following confirmation of complete response. Responding patients without complete remission should receive total of 8 cycles.

Monotherapy:

as above.

Combination with pegylated liposomal doxorubicin:

30 mg/m² pegylated liposomal doxorubicin (1h IV infusion) on day 4 of BORTEZOMIB SPC treatment cycle.

Combination with dexamethasone:

20 mg oral dexamethasone on days 1, 2, 4, 5, 8, 9, 11, and 12 of BORTEZOMIB SPC treatment cycle.

Previously untreated multiple myeloma patients not eligible for haematopoietic stem cell transplant Combination with oral melphalan (9mg/m2) and prednisone (60mg/m2):

9 x 6-weeks treatment cycles.

Previously untreated multiple myeloma patients eligible for haematopoietic stem cell transplant (induction therapy) Combination with oral dexamethasone (40mg):

4 x 21-days treatment cycles.

Combination with oral dexamethasone (40mg) and thalidomide (50mg):

4 x 28-days treatment cycles.

At least partial responders:

2 additional cycles.

For other medicinal products, see appropriate SmPCs.

Previously untreated mantle cell lymphoma not suitable for haematopoietic stem cell transplantation Combination therapy with rituximab, cyclophosphamide, doxorubicin and prednisone (VcR CAP):

6 - 8 x 21-days treatment cycles.

(For other medicinal products, see appropriate SmPCs.) Children:

Not applicable.

Hepatic Impairment:

mild - no dose adjustment; moderate or severe - start on reduced dose of 0.7 mg/m2 per injection for first cycle, then possible increase to 1.0 mg/m2 or reduction to 0.5 mg/m2 based on tolerability.

Renal Impairment:

See precautions.

Contraindications:

1. Hypersensitivity to active substance, boron or any excipients.
2. Acute diffuse infiltrative pulmonary and pericardial disease.

Special Warnings & Precautions:

- Do not administer intrathecally.
- Monitor complete blood counts; consider platelet transfusion.
- GI toxicity very common; monitor closely.
- In MCL, transient neutropenia reported between cycles; monitor for signs/symptoms of infection, treat promptly; consider prophylactic granulocyte colony stimulating factors if delayed cycles.

Herpes zoster virus reactivation:

anti-viral prophylaxis recommended. Screen for Hepatitis B Virus reactivation/infection when rituximab combination; consider antiviral prophylaxis (see SmPC for rituximab).

Very rarely John Cunningham virus infection resulting in Progressive Multifocal Leukoencephalopathy (PML) and death; monitor regularly for PML symptoms, discontinue if diagnosed.

Peripheral neuropathy common; requires careful monitoring, neurological evaluation and possible dose/schedule modification, or change to SC route.

Special care if risk factors for seizures.

Caution when history of syncope with medicinal products linked with hypotension, or dehydration due to recurrent diarrhoea/vomiting.

Discontinue treatment if Posterior Reversible Encephalopathy Syndrome (PRES) occurs.

Development/exacerbation of congestive heart failure/QT prolongation; monitor closely if cardiac risk factors.

Renal impairment common; monitor closely. Rarely acute diffuse infiltrative pulmonary disease of unknown aetiology e.g. pneumonitis, interstitial pneumonia, lung infiltration and acute respiratory distress syndrome (ARDS); baseline chest radiograph recommended.

If new/worsening pulmonary symptoms perform prompt diagnostic evaluation and treat appropriately; consider benefit/risk ratio before continuing.

Immunocomplex-mediated reactions e.g. serum sickness, polyarthritis with rash, proliferative glomerulonephritis: discontinue if severe.

Bortezomib exposure increased in moderate/severe hepatic impairment; reduce doses, closely monitor.

Patients with high pre-treatment tumour burden at risk of tumour lysis syndrome; monitor closely.

Concomitant CYP3A4-inhibitors: monitor closely. Caution with CYP3A4 or CYP2C19 substrates.

Side Effects:

Very common:

thrombocytopenia, neutropenia, anaemia, decreased appetite, neuropathies, peripheral sensory neuropathy, dysaesthesia, neuralgia, nausea, vomiting, diarrhoea, constipation, fatigue, pyrexia, asthenia. Multiple Myeloma: musculoskeletal pain. MCL: pneumonia, febrile neutropenia, leukopenia, lymphopenia, stomatitis, hair disorder.

Common:

herpes zoster (inc disseminated & ophthalmic), herpes simplex, fungal infection, hypokalaemia, hyponatraemia, blood glucose abnormal, sleep disorders & disturbances, motor neuropathy, loss of consciousness (inc syncope), dizziness, dysgeusia, vision abnormal, hypotension, orthostatic hypotension, hypertension, dyspnoea, upper/lower respiratory tract infection, cough, gastrointestinal haemorrhage (inc mucosal), dyspepsia, abdominal distension, oropharyngeal pain, abdominal pain (inc gastrointestinal and splenic pain), oral disorder, rash, pruritus, muscle spasms, pain in extremity, oedema (inc peripheral), chills, malaise, weight decreased.

Multiple Myeloma:

pneumonia, leukopenia, lymphopenia, dehydration, hypocalcaemia, enzyme abnormality, mood disorders & disturbances, anxiety disorder, lethargy, headache, eye swelling, conjunctivitis, vertigo, epistaxis, stomatitis, flatulence, hepatic enzyme abnormality, erythema, dry skin, muscular weakness, renal impairment, pain.

MCL:

sepsis (inc septic shock), Herpes virus infection, bacterial infections, hypersensitivity, diabetes mellitus, fluid retention, neuropathies, encephalopathy, peripheral sensorimotor neuropathy, autonomic neuropathy, dysacusis (inc tinnitus), cardiac fibrillation (inc atrial), arrhythmia, cardiac failure (inc left and right ventricular), myocardial ischaemia, ventricular dysfunction, hiccups, gastritis, oral ulceration, abdominal discomfort, dysphagia, gastrointestinal inflammation, hepatotoxicity (inc liver disorder), dermatitis, musculoskeletal pain, urinary tract infection, injection site reaction, hyperbilirubinaemia, protein analyses abnormal, weight increased.

Other side effects include:

tumour lysis syndrome, pulmonary hypertension, pancytopenia, anaphylactic shock/reaction, hearing impaired (up to and inc deafness), cardiovascular disorder (inc cardiogenic shock), pulmonary embolism, acute respiratory distress syndrome, colitis (inc clostridium difficile), hepatic failure. Multiple Myeloma: cardiac failure, Posterior Reversible Encephalopathy Syndrome, acute diffuse infiltrative pulmonary disorders, autonomic neuropathy, sepsis, herpes virus infection, meningitis, meningoencephalitis herpetic, Epstein-Barr virus infection, neoplasm malignant, leukaemia plasmacytic, mycosis fungoides, neoplasm benign, lymphadenopathy, febrile neutropenia, thrombocytopenic purpura, hypersensitivity, type III immune

complex mediated reaction, Cushing's syndrome, mental disorder, suicidal ideation, psychotic disorder, haemorrhage intracranial, peripheral sensory motor neuropathy, encephalopathy, neurotoxicity, cerebral haemorrhage, seizure disorders, paralysis, coma, eye haemorrhage, optic neuropathy, different degrees of visual impairment, cardiac tamponade, cardio-pulmonary arrest, cardiac fibrillation, arrhythmia, tachycardia, angina pectoris, pericarditis, cardiomyopathy, ventricular dysfunction, atrial flutter, myocardial infarction, atrioventricular block, torsade de pointes, angina unstable, cardiac valve disorders, sinus arrest, cerebrovascular accident, deep vein thrombosis, thrombophlebitis, phlebitis, vasculitis, peripheral embolism, pulmonary alveolar haemorrhage, bronchospasm, wheezing, respiratory failure, apnoea, haemoptysis, respiratory alkalosis, throat tightness, pancreatitis, haematemesis, gastro-intestinal obstruction, enteritis, megacolon, peritonitis, gastrointestinal ulceration & perforation, hepatotoxicity, hepatitis, cholestatis, hepatic haemorrhage, acute febrile neutrophilic dermatosis, toxic skin eruption, toxic epidermal necrolysis, Stevens Johnson syndrome, purpura, erythema multiforme, myopathies, rhabdomyolysis, renal failure, urinary retention, oliguria, death, multi-organ failure, ECG abnormality.

MCL:

hepatitis B infection, bronchopneumonia, autonomic nervous system imbalance, vertigo, pneumonitis, pulmonary oedema (inc acute). Refer to SmPC for other side effects.

Pregnancy:

- No clinical data available for bortezomib.
- Thalidomide contraindicated during pregnancy and in women of childbearing potential unless all conditions of thalidomide pregnancy prevention programme met.
- Male and female patients of childbearing potential must use effective contraceptive measures during treatment and for 3 months following.

Lactation:

Not recommended.

Interactions:

- Closely monitor when bortezomib is combined with potent CYP3A4-inhibitors (e.g. ketoconazole, ritonavir).
- Concomitant use of bortezomib with strong CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort) not recommended.
- Hypo/hyperglycaemia reported in diabetic patients receiving oral hypoglycaemics.

Information for Adverse Drug Reaction reporting:

The National Pharmacovigilance Centre (NPC)

Saudi Food and Drug Authority (SFDA)
SFDA call center: 19999
Toll free phone: 800 24 90000
Fax: +966-11- 205 7662
E-mail: npc.drug@sfda.gov.sa
Website: http://ade.sfda.gov.sa/

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