VELCADE® (bortezomib) in treatment of multiple myeloma

FACTSHEET

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What is VELCADE® (bortezomib)?

VELCADE® is a medicine to treat the blood cancer multiple myeloma (MM). It is the first of a type of treatment to interrupt one of the chemical messengers used to control how multiple myeloma (MM) cells grow.1

Research has shown that VELCADE used on its own can slow, reverse or halt progression of MM in patients - either as first treatment, or in patients whose disease has reappeared after a period of improvement (relapsed) and in patients whose disease has not responded to a prior treatment (refractory).1

In Europe, VELCADE® is licensed as follows: Error! Reference source not found.
- VELCADE® can be used in combination melphalan and prednisone for patients with previously untreated MM who are not eligible for high-dose chemotherapy with a bone marrow transplant.
- VELCADE® can be used on its own to treat progressive MM in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplantation.

How does VELCADE® work?

Cancer cells undergo genetic changes that result in abnormal growth and development. MM is a form of cancer affecting cells in the blood, with MM cells producing excess amounts of protein. In 2004, Irwin Rose of the United States and Aaron Ciechanover and Avram Hershko of Israel received the Nobel Prize in Chemistry for their work in uncovering the mechanism within cells that breaks down and removes abnormal proteins.2

Using the discoveries of Ciechanover, Hershko and Rose, researchers were able to develop the active substance in VELCADE®, bortezomib. Bortezomib is a proteasome inhibitor, meaning that it blocks the action of proteasomes - the cellular complexes that break down proteins. By blocking proteasomes, a build-up of protein occurs in MM cells, eventually causing their destruction. The constant division and reproduction of MM cells makes them much more sensitive to proteasome inhibition than normal cells.3

What clinical evidence supports VELCADE® indications?

Clinical efficacy in previously untreated MM:

- In 2011, an updated overall survival (OS) analysis of the landmark VISTA (VELCADE as Initial Standard Therapy in multiple myeloma: Assessment with melphalan and prednisone) trial - after 5 years of follow-up - was presented at the annual meeting of the American Society for Hematology (ASH). These data demonstrated that VELCADE (bortezomib), in combination with melphalan and prednisone (VMP), delivered a significant long-term overall survival (OS) benefit of 13.3 months (HR 0.695, p=0.0004), compared to treatment with melphalan-prednisone (MP), in patients with previously untreated MM.4

This long term, five-year follow-up analysis, reported median overall survival of nearly 5 years (56.4 months) for patients randomised to VMP compared to 3.6 years (43.1 months) [HR 0.695, p=0.0004] for patients randomised to MP, reflecting a 13.3...
In 2008, the New England Journal of Medicine published the first results from the VISTA trial, one of the largest Phase-III registration trials conducted in previously untreated multiple myeloma patients ineligible for stem cell transplantation. At this time, a survival advantage for the patients treated by VMP was already evident. The updated results, published in the Journal of Clinical Oncology in 2010, confirmed this finding and showed that patients treated with VMP do not have increased resistance to follow-on therapies at the time of relapse, as compared to patients having received MP.

Clinical efficacy in relapsed or refractory MM:

The efficacy of VELCADE® in patients whose MM has come back or not been controlled by earlier treatment has been assessed in a number of clinical trials:

- **The MMY-3021 trial**
  In 2011, results from the MMY-3021 Phase III open-label, non-inferiority trial were published in The Lancet Oncology. The study compared subcutaneous (SC) and intravenous (IV) administration of VELCADE® in relapsed multiple myeloma patients. The 222 patients with relapsed multiple myeloma were randomly assigned to receive subcutaneous or intravenous VELCADE®.

Results from the study showed that the efficacy of SC VELCADE® was similar to that of IV VELCADE®, but the frequency and severity of side effects was significantly reduced with SC compared to IV VELCADE®. The incidence of grade 3 or higher treatment-related adverse events was significantly lower in SC compared to IV administration (39% vs. 55%). Of particular note is that peripheral neuropathy (pain and tingling in the extremities) was observed in 38% of patients who received SC VELCADE® compared with 53% receiving IV VELCADE® and grade ≥3 peripheral neuropathy events were reduced from 16% in IV to 6% in SC. Lower levels of treatment discontinuations (because of adverse events) were seen, with 22% in the SC arm vs. 27% in the IV arm.

- **APEX (Assessment of Proteasome Inhibition for Extending Remission)**
  In 2005, results from the Phase III APEX trial showed a significant survival advantage with VELCADE® in patients who had received one to three earlier treatments for their MM. Treatment with VELCADE® led to a significantly longer time to progression of disease, a significantly prolonged survival and a significantly higher response rate, compared to those in the control group who received the standard therapy of high doses of a steroid called dexamethasone. There were 699 patients with relapsed MM in the APEX trial.

Both in patients who were refractory to their last prior therapy and those who were not refractory, overall survival was significantly longer and response rate was significantly higher in patients taking VELCADE.

How is VELCADE® administered?

Treatment with VELCADE® must be initiated and administrated under the supervision of a doctor who is trained and experienced in the use of chemotherapeutic agents. VELCADE® is a powder that is made up into a solution for injection, either into the vein (intravenous or IV) or under the skin (subcutaneous or SC). It is supplied in vials. The powder must be reconstituted into a solution, the concentration of which is determined by the route of administration. The appropriate concentration of VELCADE® solution is...
then given as an injection either into a vein (3-5 seconds) or under the skin (20-30 seconds), usually on a twice weekly basis over a period of two weeks, followed by a 10-day rest period. This three-week period is considered a treatment cycle.1

The 3.5 mg vial of VELCADE® can be used for either subcutaneous or IV administration. The 1 mg vial is for IV use only. The reconstitution of VELCADE® for subcutaneous and IV injection differs. The reconstituted concentration of VELCADE® for subcutaneous administration (2.5 mg/mL) is greater than the reconstituted concentration for IV administration (1 mg/mL).9

The “Information for Medical or Healthcare Professionals” section of the Package Leaflet and the Summary of Product Characteristics (SmPC) contains the complete instructions on the reconstitution and administration of VELCADE®.

What is the safety profile?

As a form of chemotherapy, VELCADE® is extremely toxic to cancer cells. However it can also cause unwanted effects, some of which can be serious. The most commonly experienced are listed below:1

Problems with cells in the blood
- Neutropenia (low levels of neutrophils, a type of white blood cell) making patients more susceptible to infections
- Thrombocytopenia (low levels of platelets) leading to an increased risk of bleeding.

Gastrointestinal problems
- VELCADE® treatment can cause nausea, vomiting, diarrhea, and constipation

Peripheral neuropathy
- VELCADE® can cause damage to the nerves, a condition called peripheral neuropathy which can lead to muscle weakness, tingling, burning, pain, and loss of feeling in your hands and feet, any of which can be severe
  - VELCADE® subcutaneous administration demonstrates a significantly lower incidence of peripheral neuropathy (PN).7

Low blood pressure
- VELCADE® can cause a drop in blood pressure leaving patients feeling dizzy or faint

Heart problems
- VELCADE® treatment can cause or worsen heart rhythm problems and heart failure

Lung Disorders
- There have been reports of lung disorders in patients receiving VELCADE. Some of these events have been fatal

Liver disease
- VELCADE® has caused sudden liver failure in patients who were taking many medications or had other serious medical conditions. It is harder for patients with pre-existing liver problems to metabolise VELCADE®

Tumor Lysis Syndrome (TLS)
- TLS is a group of metabolic conditions that can occur after cancer treatment and will be monitored for

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
- There have been reports of a rare, reversible condition involving the brain called RPLS in patients treated with VELCADE®. Patients with RPLS can have seizures, high blood
pressure, headaches, tiredness, confusion, blindness or other vision problems. VELCADE® treatment should be stopped in cases of RPLS.

VELCADE® subcutaneous administration demonstrated a significantly lower overall incidence of adverse events (AE’s) compared to IV.7 For a description of the data please see the above section on MMY-3021.

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References


4 San Miguel JF et al. Continued Overall Survival Benefit After 5 Years’ Follow-Up with Bortezomib-Melphalan-Prednisone (VMP) Versus Melphalan-Prednisone (MP) in Patients with Previously Untreated Multiple Myeloma, and No Increased Risk of Second Primary Malignancies: Final Results of the Phase 3 VISTA Trial. Presented at the 52nd American Society for Hematology (ASH) Annual Meeting, 12.12.11.


6 Mateos MV et al. Bortezombi plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: Updated follow-up and impact of subsequent therapy in the Phase III VISTA trial. JCO 2010;28(13):2259-2266. http://jco.ascopubs.org/content/28/13/2259.abstract?sid=fe102f03-9777-4e5a-8fb5-5a380b49fa6


9 Dosing information for subcutaneous and intravenous administration of VELCADE