Important information regarding

Reconstitution, dosing and administration

of **Bortezomib Actavis** (bortezomib)
3.5 mg vial for Subcutaneous (SC)
and Intravenous (IV) use

Actavis

Content

Correct reconstitution for SC and IV administration

Bortezomib Actavis 3.5 mg powder for solution for injection can be used for either intravenous or subcutaneous administration, but reconstitution is different.

There have been fatal cases of inadvertent intrathecal administration of bortezomib. Bortezomib should not be administered intrathecally.

Subcutaneous or Intravenous use only.
Do not give by other routes.
Intrathecal administration has resulted in death.

Please note: Bortezomib may also be available in other strength than the 3.5 mg vial. Please refer to the Summary of Product Characteristics (SmPC) of the relevant product for guidance on route of administration and other information.

Treatment must be initiated and administered under the supervision of a physician qualified and experienced in the use of chemotherapeutic agents. Bortezomib Actavis must be reconstituted by a Health Care Professional.
Aseptic technique must be strictly observed throughout the handling of Bortezomib Actavis, since no preservative is present.

Avoiding the potential risk of administration errors

In order to avoid dosing errors, caution is required when preparing Bortezomib Actavis as the volume required for reconstitution for the SC route is lower (1.4 ml) than that used for IV use (3.5 ml) giving a higher concentration of diluted drug (details are shown in next two sections).

As the drug concentration after reconstitution differs between the SC and IV preparations, special care is required when calculating the volume of reconstituted drug, which will be delivered to the patient according to the prescribed dose. Please see examples of dosing for the different routes in sections later in this booklet.

Subcutaneous route of administration

Preparation of the 3.5 mg vial

- **Each 3.5 mg vial of bortezomib should be reconstituted with 1.4 ml sterile sodium chloride 9 mg/ml (0.9%) solution for injection. Dissolution of the lyophilised powder is completed in less than 2 minutes.**
- **After reconstitution, each ml solution contains 2.5 mg bortezomib.**

Reconstitute the powder with 1.4 ml sodium chloride by injecting the sodium chloride solution into the vial containing the lyophilised Bortezomib Actavis.

The reconstituted solution should be clear and colourless.

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.

Reconstitution for Subcutaneous administration

Add **1.4 ml**
0.9% sodium chloride

To make **2.5 mg/ml**
final concentration

The volume of 0.9% sodium chloride used to reconstitute Bortezomib Actavis for subcutaneous administration is less than the volume used for IV administration, giving a more concentrated drug solution for injection.

- **PLEASE NOTE:** The final drug concentration, when reconstituted for SC administration (2.5 mg/ml), is 2.5 times higher than that for the IV route (1 mg/ml) and therefore the volume required is lower when the SC route of administration is used.
- Once dissolved, withdraw the appropriate amount of the reconstituted drug solution: according to calculated dose based upon the patient´s Body Surface Area (BSA). **Use caution when calculating the volume to be administered.**
- **To avoid administration errors, label the syringe (e.g. with sticker) with the intended route of administration.**

Intravenous route of administration

Preparation of the 3.5 mg vial

- **Each 3.5 mg vial of bortezomib must be reconstituted with 3.5 ml sterile sodium chloride 9 mg/ml (0.9%) solution for injection. Dissolution of the lyophilised powder is completed in less than 2 minutes.**
- **After reconstitution, each ml solution contains 1 mg bortezomib.**

Reconstitute the powder with 3.5 ml sodium chloride by injecting the sodium chloride solution into the vial containing the lyophilised Bortezomib Actavis.

The reconstituted solution is clear and colourless.

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.

Reconstitution for Intravenous administration

Add **3.5 ml**
0.9% sodium chloride

To make **1 mg/ml**
final concentration

The volume of 0.9% sodium chloride used to reconstitute Bortezomib Actavis for intravenous administration is more than the volume used for SC administration, giving a less concentrated drug solution for injection.

- Once dissolved, withdraw the appropriate amount of the reconstituted drug solution: according to calculated dose based upon the patient´s Body Surface Area (BSA). **Use caution when calculating the volume to be administered.**
- **To avoid administration errors, label the syringe (e.g. with sticker) with the intended route of administration.**

Dosing examples for SC and IV administration

- The amount (in mg) of Bortezomib Actavis to be administered is based on body surface area (BSA) calculations using a standard nomogram or according to institutional policy. < Also, the BSA can be calculated using the dosing slide rule provided with this brochure. Additional dosing examples are provided with the dosing slide rule. >
- The drug quantity contained in one vial (3.5 mg) may exceed the dose required. Use caution when calculating the dose to prevent overdose.

Calculating Bortezomib Actavis volume (ml)

$$\frac{\text{Bortezomib Actavis dose (mg/m}^2\text{)} \times \text{patient BSA (m}^2\text{)}}{\text{Reconstituted concentration}^{\dagger}} = \text{Total Bortezomib Actavis volume (ml) to be administered}$$

† 2.5 mg/ml for subcutaneous administration and 1.0 mg/ml for intravenous administration

Dosing examples for Subcutaneous and Intravenous administration

BSA: 1.7 m², Dose: 1.3 mg/m²

Intravenous Sample patient (1.7 m²)	**Subcutaneous** Sample patient (1.7 m²)
Vial size: 3.5 mg lyophilisate **Diluent volume:** 3.5 ml saline	**Vial size:** 3.5 mg lyophilisate **Diluent volume:** 1.4 ml saline
Final concentration: **1 mg/ml**	Final concentration: **2.5 mg/ml**
Dose: 1.3 mg/m² **Total dose for patient: 2.21 mg**	**Dose:** 1.3 mg/m² **Total dose for patient: 2.21 mg**
Total volume* **applied to the patient: 2.2 ml**	**Total volume*** **applied to the patient: 0.9 ml**
Injected IV (3–5 seconds push)	**Injected SC**

* Total volume rounded

BSA: 1.95 m², Dose: 1.3 mg/m²

Intravenous Sample patient (1.95 m²)	**Subcutaneous** Sample patient (1.95 m²)
Vial size: 3.5 mg lyophilisate **Diluent volume:** 3.5 ml saline	**Vial size:** 3.5 mg lyophilisate **Diluent volume:** 1.4 ml saline
Final concentration: **1 mg/ml**	Final concentration: **2.5 mg/ml**
Dose: 1.3 mg/m² **Total dose for patient: 2.54 mg**	**Dose:** 1.3 mg/m² **Total dose for patient: 2.54 mg**
Total volume* **applied to the patient: 2.5 ml**	**Total volume*** **applied to the patient: 1 ml**
Injected IV (3-5 seconds push)	**Injected SC**

* Total volume rounded

BSA: 1.6 m², Dose: 1.0 mg/m²

Intravenous Sample patient (1.6 m²)	**Subcutaneous** Sample patient (1.6 m²)
Vial size: 3.5 mg lyophilisate **Diluent volume:** 3.5 ml saline	**Vial size:** 3.5 mg lyophilisate **Diluent volume:** 1.4 ml saline
Final concentration: **1 mg/ml**	Final concentration: **2.5 mg/ml**
Dose: 1.0 mg/m² **Total dose for patient: 1.6 mg**	**Dose:** 1.0 mg/m² **Total dose for patient: 1.6 mg**
Total volume* **applied to the patient: 1.6 ml**	**Total volume*** **applied to the patient: 0.64 ml**
Injected IV (3-5 seconds push)	**Injected SC**

* Total volume rounded

Note: If the calculated IV volume is used with the SC concentration, the patient will be overdosed. If the calculated SC volume is used with the IV concentration the patient will be underdosed.

Method of administration

Bortezomib Actavis 3.5 mg powder for solution for injection IS FOR SUBCUTANEOUS OR INTRAVENOUS USE. Do not give by other routes. Intrathecal administration has resulted in death.

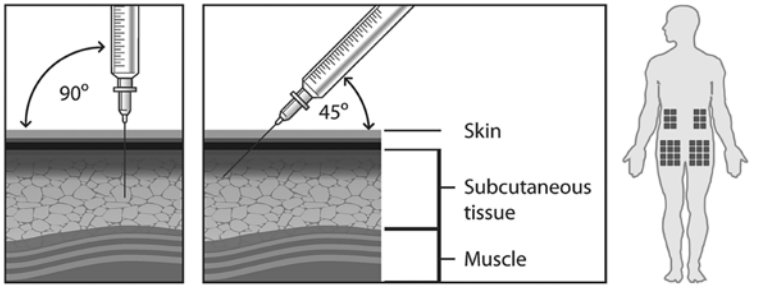
Handling and preparation of Bortezomib Actavis
Bortezomib is a cytotoxic agent. Therefore, caution should be used during handling and preparation of Bortezomib Actavis. Use of gloves and other protective clothing to prevent skin contact is recommended. **Aseptic technique** must be strictly observed throughout the handling of bortezomib, since it contains no preservative.

Intravenous administration

- Confirm the dose and concentration in the syringe prior to use **(check that the syringe is marked for intravenous administration)**.
- Inject the solution as a **3-5 second bolus intravenous injection** through a peripheral or central intravenous catheter into a vein. At least 72 hours should elapse between consecutive doses of bortezomib.
- Flush the peripheral or intravenous catheter with sterile, 9 mg/ml (0.9 %) sodium chloride solution.
- The use of IV hydration and an antiemetic medication as concomitant therapy prior to administration of IV Bortezomib Actavis is recommended.
- Remind the patient to take the antiviral prophylaxis.

Subcutaneous administration

- Confirm the dose and concentration in the syringe prior to use **(check that the syringe is marked for subcutaneous administration)**.
- Inject the solution subcutaneously, at a 45-90 °angle.
- The reconstituted solution should be administered subcutaneously in the thighs or abdomen and injection sites should be rotated for successive injections.
- If local injection site reactions occur following Bortezomib Actavis injection subcutaneously, either a less concentrated Bortezomib Actavis solution (1 mg/ml instead of 2.5 mg/ml) may be administered subcutaneously or a switch to intravenous injection is recommended.
- **Injections at the same site should be avoided**
  Alternate between
  - right and left abdomen (upper or lower quadrant)
  - right and left thigh (proximal and distal sites)
- Remind the patient to take the antiviral prophylaxis.



Storage after reconstitution

The reconstituted product is preservative free and 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. It is not necessary to protect the reconstituted medicinal product from light.

Disposal

- Each vial of Bortezomib Actavis is for only a single use. Dispose of any unused medicinal product or waste material in accordance with local requirements.
- Consider handling and disposing of Bortezomib Actavis according to guidelines issued for cytotoxic drugs, including using gloves and other protective clothing to prevent skin contact.

For full product information, please refer to the Summary of Product Characteristis (SmPC) for Bortezomib Actavis.

Call for reporting

Healthcare professionals are reminded to continue to report suspected adverse reactions associated with hydrochlorothiazide medicines in accordance with the national spontaneous reporting system. Any suspected adverse reactions and medication errors can be reported via the national Adverse Drug Reactions (ADRs) reporting system. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Post-licensing directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, Malta or sent by email to postlicensing.medicinesauthority@gov.mt

Company contact point

Should you have any questions or require additional information, please call Medical Information at:
Company : Actavis Group PTC ehf
Email: PHVMALTA@actavis.com
Phone : +30 211 880 5166

Reconstitution of Bortezomib Actavis

(bortezomib) **3.5 mg vial**

For intravenous (IV) or subcutaneous (SC) administration

Bortezomib Actavis 3.5 mg powder for solution for injection can be used for either intravenous or subcutaneous administration, but reconstitution is different

Subcutaneous administration

To reconstitute

add **1.4 ml**

of sterile 0.9% sodium chloride solution into the vial of Bortezomib Actavis for a final concentration of

2.5 mg/ml

Intravenous administration

To reconstitute

add **3.5 ml**

of sterile 0.9% sodium chloride solution into the vial of Bortezomib Actavis for a final concentration of

1 mg/ml

- The volume of diluent used to reconstitute Bortezomib Actavis for SC administration is different from the volume for IV administration. Due to the different volume added, the solutions after reconstitution differ in drug concentration.
- Bortezomib Actavis must be reconstituted by a Health Care Professional utilizing strict **aseptic techniques** since no preservative is present.
- Bortezomib is a cytotoxic agent. Therefore, caution should be used during handling and preparation of Bortezomib Actavis. Use of gloves and other protective clothing to prevent skin contact is recommended.
- The reconstituted product should be used immediately after preparation. However, the chemical and physical in-use stability of the reconstituted solution stored in the original vial and/or syringe has been demonstrated for 8 hours at 25°C. It is not necessary to protect the reconstituted medicinal product from light.
- To avoid administration errors, syringes for SC and IV use should be labelled differently, e.g. with a sticker following reconstitution.
- **Subcutaneous or Intravenous use only. Do not give by other routes.**
- Please report any adverse event experienced with the administration of Bortezomib Actavis immediately.

Please note: Bortezomib may also be available in other strength than the 3.5 mg vial. Please refer to the Summary of Product Characteristics (SmPC) of the relevant product for guidance on route of administration and other information.

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Method of administration

IV administration

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 sodium chloride 9 mg/ml (0.9%) solution for injection.

SC administration

The reconstituted solution is administered subcutaneously in the thighs (right or left, proximal and distal sites) or abdomen (right or left, upper or lower quadrant). Injection sites should be rotated for successive injections.

Reference: Moreau et al, Haemotologica 2008; 93(12)

Example

Body surface m^2	Total dose required (in mg) with 1.3 mg/m^2	Applied volume with IV use (in ml)	Applied volume with SC use (in ml)
1.5	1.95	1.95	0.78
1.6	2.08	2.08	0.83
1.7	2.21	2.21	0.88
1.8	2.34	2.34	0.94
1.9	2.47	2.47	0.99
2.0	2.60	2.60	1.04
2.1	2.73	2.73	1.09

Actavis

Bortezomib Actavis

3.5 mg powder for solution for injection

Instructions:
Set **Weight** at **Height** using the appropriate units of measure.
Read **Body Surface** Area at arrow.

Height (cm)
210 220 190 180 170 160 150 140 130 120 110 100

Weight (Kg) (lb)

Height (in)
85 80 75 70 65 60 55 50 45 40

Body Surface Area (m^2)

From the formula of Dubois and Dubois, Arch Intern Med 1916;17:863

Subcutaneous or Intravenous use only.
Do not give by other routes.

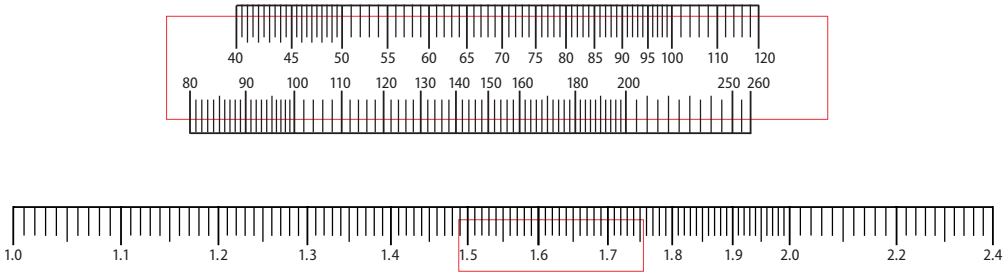
Please see Precautions and Posology and Method of Administration sections of SmPC for dose modification information.

Reconstitution of 3.5 mg Bortezomib Actavis solution for IV injection

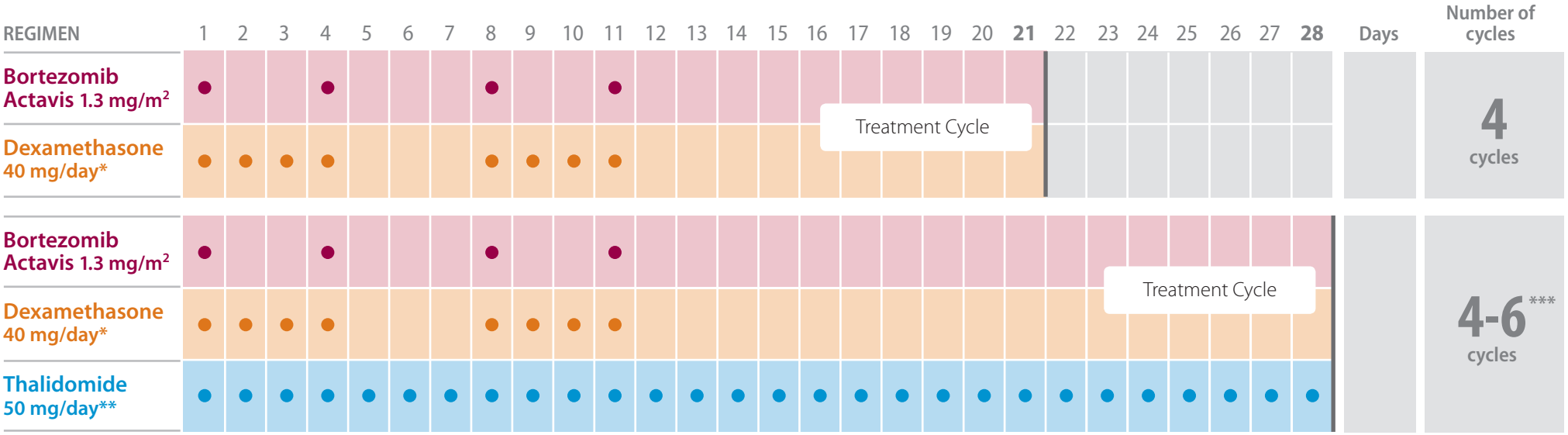
Route of administration	Pack size	Reconstitution volume	Final concentration
Intravenous use only	3.5 mg	3.5 ml	1.0 mg/ml

Reconstitution of 3.5 mg Bortezomib Actavis solution for SC injection

Route of administration	Pack size	Reconstitution volume	Final concentration
Subcutaneous use only	3.5 mg	1.4 ml	2.5 mg/ml


40 45 50 55 60 65 70 75 80 85 90 95 100 110 120
80 90 100 110 120 130 140 150 160 180 200 250 260
1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8 1.9 2.0 2.2 2.4

Bortezomib Actavis - Graph for Transplant Induction Regimens



* Dexamethasone is administered orally at 40 mg on days 1, 2, 3, 4 and 8, 9, 10, 11 of the Bortezomib Actavis 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 Actavis in combination with Thalidomide should adhere to the pregnancy prevent programme of Thalidomide. Refer to the SmPC of Thalidomide for additional information.

*** Up to 6 cycles may be given to patients who achieve at least a partial response after 4 cycles.

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