Package leaflet: Information for the user

Zegomib 1 3.5 mg, poeder voor oplossing voor injectie
Bortezomib

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zegomib is and what it is used for

Zegomib contains the active substance bortezomib, a so-called 'proteasome inhibitor'. Proteasomes play an important role in controlling cell function and growth. By interfering with their function, bortezomib can kill cancer cells.
Zegomib is used for the treatment of multiple myeloma (a cancer of the bone marrow) in patients older than 18 years:
- alone or together with the medicines pegylated liposomal doxorubicin or dexamethasone, for patients whose disease is worsening (progressive) after receiving at least one prior treatment and for whom blood stem cell transplantation was not successful or is unsuitable.
- in combination with the medicines melphalan and prednisone, for patients whose disease has not been previously treated and are unsuitable for high-dose chemotherapy with blood stem cell transplantation.
- in combination with the medicines dexamethasone or dexamethasone together with thalidomide, for patients whose disease has not been previously treated and before receiving high-dose chemotherapy with blood stem cell transplantation (induction treatment).

Zegomib is used for the treatment of mantle cell lymphoma (a type of cancer affecting the lymph nodes) in patients 18 years or older in combination with the medicines rituximab, cyclophosphamide, doxorubicin and prednisone, for patients whose disease has not been previously treated and for whom blood stem cell transplantation is unsuitable.

2. What you need to know before you use Zegomib

Do not use Zegomib
- if you are allergic to bortezomib, boron or to any of the other ingredients of this medicine (listed in section 6)
- if you have certain severe lung or heart problems.

Warnings and precautions
Talk to your doctor or pharmacist before using Zegomib, if you have any of the following:
- low numbers of red or white blood cells
- bleeding problems and/or low number of platelets in your blood

- diarrhoea, constipation, nausea or vomiting
- fainting, dizziness or light-headedness in the past
- kidney problems
- moderate to severe liver problems
- numbness, tingling, or pain in the hands or feet (neuropathy) in the past
- heart or blood pressure problems
- shortness of breath or cough
- seizures
- shingles (localised including around the eyes or spread across the body)
- symptoms of tumor lysis syndrome such as muscle cramping, muscle weakness, confusion, visual loss or disturbances and shortness of breath
- memory loss, trouble thinking, difficulty with walking or loss of vision. These may be signs of a serious brain infection and your doctor may suggest further testing and follow-up.

You will have to take regular blood tests before and during your treatment with Zegomib, to check your blood cell counts regularly.
If you have mantle cell lymphoma and are given the medicine rituximab with Zegomib you should tell your doctor:

- if you think you have hepatitis infection now or have had it in the past. In a few cases, patients who have had hepatitis B might have a repeated attack of hepatitis, which can be fatal. If you have a history of hepatitis B infection you will be carefully checked by your doctor for signs of active hepatitis B.

You must read the package leaflets of all medicinal products to be taken in combination with Zegomib for information related to these medicines before starting treatment with Zegomib. When thalidomide is used, particular attention to pregnancy testing and prevention requirements is needed (see Pregnancy and breast-feeding in this section).

Children and adolescents
Zegomib should not be used in children and adolescents because it is not known how the medicine will affect them.

Other medicines and Zegomib
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines, including medicines obtained without a prescription.
In particular, tell your doctor if you are using medicines containing any of the following active substances:

- ketoconazole, used to treat fungal infections
- ritonavir, used to treat HIV infection
- rifampicin, an antibiotic used to treat bacterial infections
- carbamazepine, phenytoin or phenobarbital used to treat epilepsy
- St. John's Wort (Hypericum perforatum), used for depression or other conditions
- oral antidiabetics

Pregnancy and breast-feeding
You should not use Zegomib if you are pregnant, unless clearly necessary.
Both men and women receiving Zegomib must use effective contraception during and for up to 3 months after treatment. If, despite these measures, pregnancy occurs, tell your doctor immediately.
You should not breast-feed while using Zegomib. Discuss with your doctor when it is safe to restart breast-feeding after finishing your treatment.

Thalidomide causes birth defects and foetal death. When Zegomib is given in combination with thalidomide you must follow the pregnancy prevention programme for thalidomide (see package leaflet for thalidomide).

Driving and using machines
Zegomib might cause tiredness, dizziness, fainting, or blurred vision. Do not drive or operate tools or machines if you experience such side effects; even if you do not, you should still be cautious.

3. How to use Zegomib

Your doctor will work out your dose of Zegomib according to your height and weight (body surface area). The recommended starting dose of Zegomib is 1.3 mg/m^2 body surface area twice a week. Your doctor may change the dose and total number of treatment cycles, depending on your response to the treatment on the occurrence of certain side effects and on your underlying conditions (e.g. liver problems).

Progressive multiple myeloma
When Zegomib is given alone, you will receive 4 doses of Zegomib intravenously or subcutaneously on days 1, 4, 8 and 11, followed by a 10-day 'rest period' without treatment. This 21-day period (3 weeks) corresponds to one treatment cycle. You might receive up to 8 cycles (24 weeks).

You may also be given Zegomib together with the medicines pegylated liposomal doxorubicin or dexamethasone.

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

When Zegomib is given together with dexamethasone, you will receive Zegomib 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 the Zegomib, 21-day treatment cycle.
You might receive up to 8 cycles (24 weeks).

Previously untreated multiple myeloma
If you have not been treated before for multiple myeloma, and **you are not** suitable for blood stem cell transplantation you will receive Zegomib intravenously together with two other medicines, melphalan and prednisone.
In this case, the duration of a treatment cycle is 42 days (6 weeks). You will receive 9 cycles (54 weeks).

- In cycles 1 to 4, Zegomib is administered twice weekly on days 1, 4, 8, 11, 22, 25, 29 and 32.
- In cycles 5 to 9, Zegomib 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.

If you have not been treated before for multiple myeloma, and **you are** suitable for blood stem cell transplantation you will receive Zegomib intravenously or subcutaneously together with the medicines dexamethasone, or dexamethasone and thalidomide, as induction treatment.

When Zegomib is given together with dexamethasone, you will receive Zegomib 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 Zegomib 21-day treatment cycle.

You will receive 4 cycles (12 weeks).

When Zegomib 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 Zegomib 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.
You might receive up to 6 cycles (24 weeks).

Previously untreated mantle cell lymphoma
If you have not been treated before for mantle cell lymphoma you will receive Zegomib intravenously together with the medicines rituximab, cyclophosphamide, doxorubicin and prednisone.
Zegomib is given intravenously 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). You might receive up to 8 cycles (24 weeks).
The following medicinal products are given on day 1 of each Zegomib 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 Zegomib treatment cycle.

How Zegomib is given
This medicine is for intravenous or subcutaneous use. Zegomib will be administered by a health care professional experienced in the use of cytotoxic medicines.
Zegomib powder has to be dissolved before administration. This will be done by a healthcare professional. The resulting solution is then either injected into a vein or under the skin. Injection into a vein is rapid, taking 3 to 5 seconds. Injection under the skin is in either the thighs or the abdomen.

If you are given too much Zegomib
As this medicine is being given by your doctor or nurse, it is unlikely that you will be given too much. In the unlikely event of an overdose, your doctor will monitor you for side effects.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some of these effects may be serious.

If you are given Zegomib for multiple myeloma or mantle cell lymphoma, tell your doctor straight away if you notice any of the following symptoms:
- muscle cramping, muscle weakness
- confusion, visual loss or disturbances, blindness, seizures, headaches
- shortness of breath, swelling of your feet or changes in your heart beat, high blood pressure, tiredness, fainting
- coughing and breathing difficulties or tightness in the chest.

Treatment with Zegomib can very commonly cause a decrease in the numbers of red and white blood cells and platelets in your blood. Therefore, you will have to take regular blood tests before and during your treatment with Zegomib, to check your blood cell counts regularly. You may experience a reduction in the number of:
- platelets, which may make you be more prone to bruising, or to bleeding without obvious injury (e.g., bleeding from your bowels, stomach, mouth and gum or bleeding in the brain or bleeding from the liver)
- red blood cells, which can cause anaemia, with symptoms such as tiredness and paleness
- white blood cells may make you more prone to infections or flu-like symptoms

If you are given Zegomib for the treatment of multiple myeloma the side effects you may get are listed below:

Very common side effects (may affect more than 1 in 10 people)
- Reduction in the number of platelets, white blood cells and/or red blood cells (see above)
- Loss of appetite
- Sensitivity, numbness, tingling or burning sensation of the skin, or pain in the hands or feet, due to nerve damage
- Feeling sick (nausea) or vomiting
- Constipation
- Diarrhoea: if this happens, it is important that you drink more water than usual. Your doctor may give you medicine to control diarrhoea
- Muscle pain, bone pain
- Fever, tiredness (fatigue), feeling weak

Common side effects (may affect up to 1 in 10 people)
- Shingles (localised including around the eyes or spread across the body), pneumonia, herpes virus infection, fungal infection
- Dehydration
- Reduction of the blood level of potassium, sodium and calcium, abnormal blood sugar levels, abnormal blood enzyme levels
- Mood swings, anxiety, difficulty or problems in sleeping
- Muscular dystrophy due to damage of nerves controlling muscle function
- Loss of consciousness, fainting, dizziness
- Dysfunction of taste
- Lethargy
- Headache
- Swelling of the eyes, vision disorder, infection of the outermost layer of the eye and the inner surface of the eyelids (conjunctivitis)
- Vertigo
- Low blood pressure, sudden fall of blood pressure on standing which may lead to fainting
- High blood pressure
- Shortness of breath
- Nose bleeds
- Airway infection, cough
- Bleeding from bowels or stomach, indigestion, bloating, flatulence, abdominal pain, inflammation of the mouth, mouth pain and sore throat, mouth diseases
- Alteration of liver function
- Skin rash, itching of the skin, redness of the skin, dry skin
- Muscle spasms, pain in the limbs, muscle weakness
- Damage of the kidneys
- Swelling of body, to include around eyes and other parts of the body
- Shivering, pain, general ill feeling
- Weight loss

Uncommon side effects (may affect up to 1 in 100 people)
- Infections, including infection of the brains and meninges, eyelid sty (hordeolum), the flu, skin infection, ear infection, tooth infection
- Introduction of bacteria into the bloodstream (sepsis)
- Inflammation of the connective tissue under the skin (cellulitis)
- Problems with blood clotting, increased number of white blood cells in your blood, swelling of your lymph glands, anaemia due to the damage of red blood cells

- Swelling of the face, eyes, lips and tongue, which can cause difficulties in breathing and swallowing (angioedema), allergic reactions
- Overactive adrenergic cortex (Cushing syndrome)
- Overactive thyroid gland
- Hormone abnormality which may affect salt and water absorption (antidiuretic hormone secretion disorder)
- Symptoms due to disintegration of tumor cells (called tumor lysis syndrome)
- Growth disturbances
- Decreased blood levels of magnesium, phosphate, increased blood levels of potassium, calcium and sodium, abnormal blood levels of uric acid
- Diabetes
- Fluid retention
- Mental diseases, hallutination, abnormal perception of the outher world called psychotic disorders, confusion, restlessness
- Trembling, movement disorders, loss of memory, brain damage (encephalopathies), conditions associated with seizures , pain on the affected area after herpes virus infection due to nerve damage, speech disorders
- Painful, tingling sensation in the leg which occurs mainly at night and cause urge to move legs (restless leg syndrome), migraine, inflammation of the sciatic nerve, attention disturbances, abnormal muscle reflexes, smelling disorders
- Bloodshot eye, eyelid infection, lump in the eyelid (chalazion) and red and swollen eyelids, eye inflammation, double vision, dry eyes, eye irritation, painful eyes, excessive secretion of tears, discharge from the eyes
- Hearing disorders (including ringing in the ears), hearing loss (including deafness), ear discomfort
- Fluid around the heart, circulation and breathing arrest, heart beat abnormalities (including irregular and fast heartbeat, e.g. atrial fibrillation, or fast heartbeat, palpitations, slow heartbeat)
- Heart failure, chest pain, inflammation of the lining around your heart, heart muscle diseases, abnormal function of heart ventricles
- Cerebrovascular disorders
- Blood clots in your veins, bleeding, inflammation of a vein with or without blood clot, circulatory collapse, flush, discolouration of the skin because of tissue bleeding, reduced blood flow in the limbs
- Inflammation of vessels which can appear on the skin as small red or purple dots or even bruise-like spots (usually on the legs), blood congestion (including also the eyes)
- Blood clot in the lungs, fluid in the thorax, fluid in the lungs, bleeding in the lungs, bronchial spasm, chronic obstructive pulmonary disease (COPD), reduction of blood oxygen levels, congestion in the airways, lack of oxygen, inflammation of the lining around the lungs, hiccups, runny nose, phonation disorder, wheezing
- Inflammation of the pancreas, vomiting of blood, swelling lips, blockade of the stomach or bowels, abdominal discomfort, mouth ulcers, bowel infection, stomach infection
- Bleeding gums, heartburn (reflux disease), inflammation of large intestine, inflammation and disease of the stomach and bowels, difficulty swallowing, irritable bowel disease, coated tongue, motility disorders of the intestines, diseases of salivary glands
- Liver damage, inflammation of the liver (which may cause yellow discolouration of the skin and eyes), obstruction of bile flow
- Skin reactions (e.g. erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome), which may be severe and life-threatening
- Hives, skin inflammation
- Hair disorders
- Point-like hemorrhages on the skin, bruising, skin bleeding
- Psoriasis

- Increased or night sweating, bedsore, acne, skin blisters, skin pigmentation abnormalities
- Muscle twitching, joint swelling, inflammation of the joints, joint stiffness, muscle diseases, sense of heaviness
- Renal failure, urinary tract infection, urinary tract abnormalities, blood in the urine, retention of urine, micturition disorders, protein in the urine, increased or decreased urine production (due to kidney damage), very frequent urination
- Vaginal bleeding, genital pain, problem having an erection
- General physical health deterioration, swelling of face, redness or pain at the injection site, mucosal diseases, walking disorders, feeling cold, fluid exits from the blood vessel resulting in swelling, catheter device related complications
- Thirst change
- Chest discomfort, feeling of body temperature change
- Increased blood levels of bilirubin, abnormal test results
- Weight increase
- Falls and bruises

Rare side effects (may affect up to 1 in 1,000 people)
- Fatigue syndrome after virus infection
- Cancer, including blood and lymphatic system cancer, benign tumor
- Increased number of platelets in the blood, circulatory disorders caused by excessive viscosity of blood (hyperviscosity syndrome), platelet disorders, blood clot in small blood vessels (thrombotic microangiopathy), blood disorders
- Serious allergic reaction (anaphylactic shock) signs of which may include difficulty breathing, chest pain or chest tightness, and/or feeling dizzy/faint, severe itching of the skin or raised lumps on the skin, swelling of the face, lips, tongue and /or throat, which may cause difficulty in swallowing, collapse
- Abnormal protein deposits in your vital organs (amyloidosis)
- Other immune reactions
- Underactive thyroid gland
- Increased blood level of magnesium, acidic change of blood pH, abnormalities of electrolyte blood levels, fluid overload, reduced and increased blood levels of chloride ions, decrease in the volume of circulated blood, increased blood level of phosphate, metabolic disorders, lack of Vitamin B, gout
- Increased appetite
- Inability to tolerate alcohol consumption
- Suicidal ideation, adjustment disorder, disturbance of consciousness (delirium), decreased sex drive
- Bleeding in the brain, swelling of the brain, coma, autonomic nervous system imbalance (symptoms: increased heart beat and pulse, sweating), cranial nerve palsy, paralysis, condition just before fainting, brain stem diseases, damage of the spinal nerve, nervous system diseases
- Serious nerve inflammation, which may cause paralysis and difficulty breathing (Guillain-Barré syndrome)
- Agitation
- Spinal cord compression
- Disturbance of thinking ability
- Drooling
- Reduced muscle tone
- Corneal injury, bulging eyes, inflammation of the retina, visual field defect, so-called blind spot vision (scotoma), eye diseases, tear gland inflammation, avoid of the light (photophobia), vision of flashing lights (photopsia), damage of the optic nerve, partial or total loss of vision
- Bleeding from the ear, inflammation of the vestibular nerve, ear disorders
- Heart attack, heart conduction disorders, cardiovascular diseases
- Arterial blood clots, paleness, abnormal vessel dilatation in the limbs accompanied with pain

and redness (erythromelalgia), dilatation of the vessels, discoloration of the veins, vein insufficiency
- Respiratory failure, transient cessation of respiration, pneumothorax, collapse of the lung, hypertension in lung arteries, bloody sputum, increased rate of respiration, increased difficulty breathing when lying down, change of blood pH due to breathing disorders
- Lung and bronchial diseases, reduced level of blood carbon dioxide
- Tightness in the throat, dry throat, increased upper airway secretion, throat irritation
- Inflammation of the peritoneum, swollen tongue, fluid accumulation in the abdominal cavity, inflammation of the oesophagus, inflammation of the lips, fecal incontinence, anal sphincter abnormalities, stool mass lumps in the large bowels, perforation of stomach or bowel ulcer, swollen gums, dilatation of large bowels, rectal discharge
- Blisters in the mouth or throat, painful lips, inflammation of the gums
- Anal fissure, changes of bowel habit, rectal pain, abnormal stool
- Liver failure (which can lead to yellowish discolouration of the skin and eyes), swelling of the liver, Budd-Chiari syndrome (the clinical symptoms caused by blockage of the hepatic veins), bleeding from the liver, gallstones
- Skin diseases, nail disorders (brittle or weak nails)
- Breakdown of muscle fibers leading to other complications, jaw joint disorders, fistula, joint effusion, painful jaw joint, bone disorders, musculoskeletal infections and inflammations, cysts in the lining of joints (synovial cysts)
- Bladder irritation
- Testis diseases, inflammation of the prostate gland, breast disorders in females, painful epididymal tenderness, inflammation of the epididymis, pelvic pain, vulval ulceration
- Incomplete development of an organ or body part, developmental disorder of the stomach or bowels, rough and thick dry skin
- Death, multi-organ failure, injection site bleeding, hernia, delayed wound healing, inflammation, inflammation of vessel at injection site, tenderness, ulcer, irritability, sensation of foreign body
- Abnormal blood tests (including abnormal blood oxygen and carbon dioxide levels, abnormal levels of the coagulation parameter INR, decreased pH of stomach acid, abnormal levels of troponin-I which is the indicator of heart muscles damage, abnormal virus identification results and virus antibody levels, abnormal urinary test results)
- ECG abnormalities
- Increased aggregation of platelets (can lead to blood clots)
- Abnormal reaction to blood transfusions, fracture, increased muscle tone, different type of injuries
- Increased activity of certain white blood cells, called macrophages.

If you are given Zegomib together with other medicines for the treatment of mantle cell lymphoma the side effects you may get are listed below:

Very common side effects (may affect more than 1 in 10 people)
- Pneumonia
- Reduction of the number of platelets, reduced white blood cells number with or without fever, anaemia
- Loss of appetite
- Sensitivity, numbness, tingling or burning sensation of the skin, or pain in the hands or feet, due to nerve damage
- Nausea and vomiting
- Diarrhoea
- Inflammation of the mouth
- Constipation
- Hair loss and abnormal hair texture

- Fever
- Tiredness, feeling weak

Common side effects (may affect up to 1 in 10 people)
- Introduction of bacteria into the bloodstream (sepsis)
- Shingles (localized including around the eyes or spread across the body)
- Infections, including respiratory infections
- Hypersensitivity (allergic reaction)
- Reduced blood levels of potassium, sodium, abnormal blood sugar levels,
- Diabetes
- Fluid retention
- Difficulty or problems in sleeping
- Nerve damage (neuropathy), such as motor neuropathy (symptoms: muscle atrophy, muscle weakness), or autonomic neuropathy (symptoms include increased heart rate, high blood pressure, sweating)
- Loss of conciousness, fainting
- Brain damage (encephalopathy, symptoms may be altered level of consciousness, confusion)
- Feeling dizzy
- Taste disorders
- Abnormal vision
- Abnormal hearing, ringing in the ears
- Heart rhythm disorders, heart failure, insufficient blood supply of the heart muscle, abnormal function of heart ventricles
- High or low blood pressure
- Sudden fall of blood pressure upon standing which may lead to fainting
- Shortness of breath
- Cough
- Hiccups
- Bleeding from your bowels or stomach
- Abdominal discomfort (pain, bloating)
- Indigestion, mouth and throat pain
- Mouth ulcer
- Difficulty swallowing
- Infection or inflammation of the stomach and intestines
- Stomach pain
- Mouth disease
- Liver damage
- Itching of skin
- Inflamed skin
- Skin rash
- Muscle spasms
- Muscle pain, bone pain
- Pain in limbs
- Infection of the urinary tract
- Swelling of body, to include eyes and other parts of the body
- Shivering
- Injection site reactions (e.g. redness and pain)
- General ill feeling
- Increased level of bilirubin in blood, abnormal protein test results
- Weight loss
- Weight increase

Uncommon side effects (may affect up to 1 in 100 people)

- Inflammation of the liver
- Severe allergic reaction (anaphylactic reaction) signs of which may include difficulty breathing, chest pain or chest tightness, and/or feeling dizzy/faint, severe itching of the skin or raised lumps on the skin, swelling of the face, lips, tongue and /or throat, which may cause difficulty in swallowing, collapse
- Symptoms due to disintegration of tumor cells (called tumor lysis syndrome)
- Vertigo
- Hearing impairment, deafness
- Cardiovascular disorders
- Breathing failure, blood clots in your lungs, hypertension in lung arteries, fluid in the lungs (disorders that affect your lungs, preventing your body from getting enough oxygen, symptoms may be difficulty breathing, shortness of breath with or without exercise, breathing that becomes shallow, difficult or stops, wheezing)
- Large intestine inflammation
- Blood clots in your lungs
- Liver failure (which may cause yellow discoloration of the eyes and skin
- Lump in the eyelid (chalazion), red and swollen eyelids

Rare side effects (may affect up to 1 in 1,000 people)

- Blood clot in small blood vessels (thrombotic microangiopathy)
- Serious nerve inflammation, which may cause paralysis and difficulty breathing (Guillain-Barré syndrome)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [to be completed nationally]. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zegomib

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the vial and the carton after EXP.

Keep the vial in the outer carton in order to protect from light.
This medicine does not require any special temperature storage conditions.

Reconstituted solution
Chemical and physical stability has been demonstrated for 8 hours at 25 °C/60%RH in the dark both in a vial and in a polypropylene syringe.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 ° to 8 °C, unless reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions.
Zegomib is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What Zegomib contains

- The active substance is bortezomib. Each vial contains 1 3.5 mg of bortezomib (as a mannitol

boronic ester). After reconstitution, 1 ml of solution for injection contains 1 mg bortezomib.
- The other ingredient is mannitol (E421).

Intravenous reconstitution:
After reconstitution, 1 ml of solution for intravenous injection contains 1 mg bortezomib.
Subcutaneous reconstitution:
After reconstitution, 1 ml of solution for subcutaneous injection contains 2.5 mg bortezomib.

What Zegomib looks like and contents of the pack
Zegomib powder for solution for injection is a white to off-white cake or powder.

Zegomib is packed in a glass vial with rubber stopper and a green flip-off cap.
Each pack contains 1 single-use vial.
Zegomib is packed in a glass vial with rubber stopper and a blue flip-off cap.
Pack size: 1 single-use vial or 3 single-use vials in carton box. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Houder van de vergunning voor het in de handel brengen:
Egis Pharmaceuticals PLC
1106 Budapest, Keresztúri út 30-38.
Hongarije

Fabrikanten:
Synthon Hispania SL
C/ Castelló no1, Pol. Las Salinas, Sant Boi de Llobregat,
Barcelona
08830 Spanje

Synthon s.r.o
Brnenska 32/c.p.597, Blansko
67801 Tsjechië

Egis Pharmaceuticals PLC
1165 Budapest, Bökényföldi út 118-120.
Hongarije

Zegomib 1 mg, poeder voor oplossing voor injectie: RVG 115399
Zegomib 3,5 mg, poeder voor oplossing voor injectie: RVG 115400

This medicinal product is authorised in the Member States of the EEA under the following names:

Nederland:	Zegomib 1 mg poeder voor oplossing voor injectie Zegomib 3.5 mg poeder voor oplossing voor injectie
Bulgarije:	Zegomib 1 mg прах за инжекционен разтвор Zegomib 3.5 mg прах за инжекционен разтвор
Bohemen:	Zegomib 3.5 mg
Hongarije:	Zegomib 1 mg por oldatos injekcióhoz Zegomib 3.5 mg por oldatos injekcióhoz
Roemenië:	Zegomib 1 mg pulbere pentru soluţie injectabilă Zegomib 3.5 mg pulbere pentru soluţie injectabilă

Slowakije:	Zegomib 1 mg Zegomib 3.5 mg

Deze bijsluiter is voor het laatst goedgekeurd in februari 2021.

The following information is intended for healthcare professionals only:

1 RECONSTITUTION FOR INTRAVENOUS INJECTION

Note: Zegomib is a cytotoxic agent. Therefore, caution should be used during handling and preparation. Use of gloves and other protective clothing to prevent skin contact is recommended.
ASEPTIC TECHNIQUE MUST BE STRICTLY OBSERVED THROUGHOUT HANDLING OF Zegomib SINCE NO PRESERVATIVE IS PRESENT.

1.1 **Preparation of the 1 3.5 mg vial: carefully add 1.0 3.5 ml** of sterile, 9 mg/ml (0.9%) sodium chloride solution for injection to the vial containing the Zegomib powder by using a 1 ml syringe for the preparation of the 1 mg vial, or a syringe of the appropriate size for the preparation of the 3.5 mg vial without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.
The concentration of the resulting solution will be 1 mg/ml. The solution will be clear and colourless, with a final pH of 4 to 7. You do not need to check the pH of the solution.

1.2 Before administration, visually inspect the solution for particulate matter and discolouration. If any discolouration or particulate matter is observed, the solution should be discarded. Be sure that the correct dose is being given for the **intravenous route** of administration (1 mg/ml).

1.3 The reconstituted solution is preservative free and should be used immediately after preparation. However, the chemical and physical in-use stability has been demonstrated for 8 hours at 25°C in the dark 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. If the reconstituted solution is not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

It is not necessary to protect the reconstituted medicinal product from light.

2 ADMINISTRATION

- Once dissolved, withdraw the appropriate amount of the reconstituted solution according to calculated dose based upon the patient´s Body Surface Area.
- Confirm the dose and concentration in the syringe prior to use (check that the syringe is marked as intravenous administration).
- Inject the solution as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter into a vein.
- Flush the peripheral or intravenous catheter with sterile, 9 mg/ml (0.9%) sodium chloride solution.

Zegomib 1 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.

3 DISPOSAL

A vial is for single use only and the remaining solution must be discarded.
Any unused product or waste material should be disposed of in accordance with local requirements.

The following information is intended for healthcare professionals only:
Only the 3.5 mg vial can be administered subcutaneously, as described below.

1 RECONSTITUTION FOR SUBCUTANEOUS INJECTION

Note: Zegomib is a cytotoxic agent. Therefore, caution should be used during handling and preparation. Use of gloves and other protective clothing to prevent skin contact is recommended.
ASEPTIC TECHNIQUE MUST BE STRICTLY OBSERVED THROUGHOUT HANDLING OF Zegomib SINCE NO PRESERVATIVE IS PRESENT.

1.1 **Preparation of the 3.5 mg vial: carefully add 1.4 ml** of sterile, 9 mg/ml (0.9%) sodium chloride solution for injection to the vial containing the Zegomib powder 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.
The concentration of the resulting solution will be 2.5 mg/ml. The solution will be clear and colourless, with a final pH of 4 to 7. You do not need to check the pH of the solution.

1.2 Before administration, visually inspect the solution for particulate matter and discolouration. If any discolouration or particulate matter is observed, the solution should be discarded. Be sure that the correct dose is being given for the **subcutaneous route** of administration (2.5 mg/ml).

1.3 The reconstituted product is preservative free and should be used immediately after preparation. However, the chemical and physical in-use stability has been demonstrated for 8 hours at 25°C in the dark 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. If the reconstituted solution is not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

It is not necessary to protect the reconstituted medicinal product from light.

2. ADMINISTRATION

- Once dissolved, withdraw the appropriate amount of the reconstituted solution according to calculated dose based upon the patient´s Body Surface Area.
- Confirm the dose and concentration in the syringe prior to use. (check that the syringe is marked as subcutaneous administration).
- Inject the solution subcutaneously, under a 45-90°angle.
- The reconstituted solution is administered subcutaneously through 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 Zegomib injection subcutaneously, either a less concentrated Zegomib solution (1 mg/ml instead of 2.5 mg/ml) may be administered subcutaneously or a switch to intravenous injection is recommended.

Zegomib 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.

3. DISPOSAL

A vial is for single use only and the remaining solution must be discarded.
Any unused product or waste material should be disposed of in accordance with local requirements.