Package leaflet: Information for the user

BESPONSA 1 mg powder for concentrate for solution for infusion
inotuzumab ozogamicin

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What BESPONSA is and what it is used for

The active ingredient in BESPONSA is inotuzumab ozogamicin. This belongs to a group of medicines that target cancer cells. These medicines are called antineoplastic agents.

BESPONSA is used to treat adults with acute lymphoblastic leukaemia. Acute lymphoblastic leukaemia is a cancer of blood where you have too many white blood cells. BESPONSA is intended for the treatment of acute lymphoblastic leukaemia for adult patients who have previously tried other treatments and for whom those treatments have failed.

BESPONSA acts by attaching to cells with a protein called CD22. Lymphoblastic leukaemia cells have this protein. Once attached to the lymphoblastic leukaemia cells, the medicine delivers a substance into the cells that interferes with the cells' DNA and eventually kills them.

2. What you need to know before you are given BESPONSA

Do not use BESPONSA if you:

- are allergic to inotuzumab ozogamicin or any of the other ingredients of this medicine (listed in section 6).
- have previously had severe venoocclusive disease (a condition in which the blood vessels in the liver become damaged and blocked by blood clots) which was confirmed or have ongoing venoocclusive disease.
- have serious ongoing liver disease, e.g., cirrhosis (a condition in which the liver does not function properly due to long-term damage), nodular regenerative hyperplasia (a condition with signs and symptoms of portal hypertension that can be caused by chronic use of medicines), active hepatitis (a disease characterised by inflammation of the liver).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using BESPONSA if you:

- have a history of liver problems or liver diseases or if you have signs and symptoms of a serious condition called hepatic venoocclusive disease, a condition in which the blood vessels in the liver become damaged and blocked by blood clots. Venoocclusive disease may be fatal and is associated with rapid weight gain, pain in the upper right side of your abdomen (belly), increase in the size of the liver, build-up of fluid causing abdominal swelling, and blood tests showing increases in bilirubin and/or liver enzymes (that may result in yellowing of the skin or eyes). This condition may occur during treatment with BESPONSA or after subsequent treatment with a stem cell transplant. A stem cell transplant is a procedure to transplant another person's stem cells (cells which develop into new blood cells) into your bloodstream. This procedure may take place if your disease responds completely to treatment.
- have signs or symptoms of a low number of blood cells known as neutrophils (sometimes accompanied with fever), red blood cells, white blood cells, lymphocytes, or a low number of blood components known as platelets; these signs and symptoms include developing an infection or fever or bruising easily or getting frequent nose bleeds.
- have signs and symptoms of an infusion related reaction, such as fever and chills or breathing problems during or shortly after the BESPONSA infusion.
- have signs and symptoms of tumour lysis syndrome, which may be associated with symptoms in the stomach and intestines (for example, nausea, vomiting, diarrhoea), heart (for example, changes in the rhythm), kidney (for example, decreased urine, blood in urine), and nerves and muscles (for example, muscular spasms, weakness, cramps), during or shortly after the BESPONSA infusion.
- have a history of, or tendency to have, QT interval prolongation (a change in electrical activity of the heart that can cause serious irregular heart rhythms), are taking medicines that are known to prolong QT interval, and/or have abnormal electrolyte (e.g., calcium, magnesium, potassium) levels.
- have elevations in amylase or lipase enzymes that may be a sign of problems with your pancreas or liver and gallbladder or bile ducts.

Tell your doctor, pharmacist or nurse immediately if you became pregnant during the period of treatment with BESPONSA and for up to 8 months after finishing treatment.

Your doctor will take regular blood tests to monitor your blood counts during treatment with BESPONSA. See also section 4.

During treatment, especially in the first few days after starting treatment, your white blood cell count may be severely lowered (neutropenia), which may be accompanied by fever (febrile neutropenia).

During treatment, especially in the first few days after starting treatment, you may have raised liver enzymes. Your doctor will take regular blood tests to monitor your liver enzymes during treatment with BESPONSA.

Treatment with BESPONSA may prolong QT interval (a change in electrical activity of the heart that can cause serious irregular heart rhythms). Your doctor will take an electrocardiogram (ECG) and blood tests to measure electrolytes (e.g., calcium, magnesium, potassium) before the first dose of BESPONSA and repeat these tests during treatment. See also section 4.

Your doctor will also monitor for signs and symptoms of tumour lysis syndrome after you receive BESPONSA. See also section 4.

Children and adolescents

BESPONSA should not to be used in children and adolescents under 18 years of age because no data are available in this population.

Other medicines and BESPONSA

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or nurse for advice before taking this medicine.

Contraception

You must avoid becoming pregnant or fathering a child. Women must use effective contraception during treatment and for at least 8 months after the last dose of treatment. Men must use effective contraception during treatment and for at least 5 months after the last dose of treatment.

Pregnancy

The effects of BESPONSA in pregnant women are not known, but based on its mechanism of action BESPONSA may harm your unborn baby. You should not use BESPONSA during pregnancy, unless your doctor thinks that it is the best medicine for you.

Contact your doctor immediately if you or your partner becomes pregnant during the period of treatment with this medicine.

Fertility

Men and women should seek advice regarding fertility preservation before treatment.

Breast-feeding

If you need treatment with BESPONSA, you must stop breast-feeding during treatment and for at least 2 months after treatment. Talk to your doctor.

Driving and using machines

If you feel unusually tired (this is a very common side effect of BESPONSA), you should not drive or use machines.

3. How BESPONSA is given

Always use this medicine exactly as your doctor, pharmacist, or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

How BESPONSA is given

- Your doctor will decide on the correct dose.
- A doctor or nurse will give you BESPONSA through a drip in your vein (intravenous infusion) which will run for 1 hour.
- Each dose is given weekly and each treatment cycle is 3 doses.
- If the medicine works well and you are going to receive a stem cell transplant (see section 2), you may receive 2 cycles or a maximum of 3 cycles of treatment.
- If the medicine works well, but you are not going to receive a stem cell transplant (see section 2), you may receive up to a maximum of 6 cycles of treatment.
- If you do not respond to the medicine within 3 cycles, your treatment will be stopped.

- Your doctor may change your dose, interrupt, or completely stop treatment with BESPONSA if you have certain side effects.
- Your doctor may lower your dose based on your response to treatment.
- Your doctor will do blood tests during the treatment to check for side effects and for response to treatment.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

Medicines given before treatment with BESPONSA

Before your treatment with BESPONSA, you will be given other medicines (pre-medications) to help reduce infusion reactions and other possible side effects. These may include corticosteroids (e.g., dexamethasone), antipyretics (medicines to reduce fever), and antihistamines (medicines to reduce allergic reactions).

Before your treatment with BESPONSA, you may be given medicines and be hydrated to prevent tumour lysis syndrome from occurring. Tumour lysis syndrome is associated with a variety of symptoms in the stomach and intestines (for example, nausea, vomiting, diarrhoea), heart (for example, changes in the rhythm), kidney (for example, decreased urine, blood in urine), and nerves and muscles (for example, muscular spasms, weakness, cramps).

4. Possible side effects

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

Tell your doctor immediately if you have signs and symptoms of any of the following serious side effects:

- infusion related reaction (see section 2); signs and symptoms include fever and chills or breathing problems during or shortly after the BESPONSA infusion.
- venoocclusive liver disease (see section 2); signs and symptoms include rapid weight gain, pain in the upper right side of your abdomen, increase in the size of the liver, accumulation of fluid causing abdominal swelling, and increases in bilirubin and/or liver enzymes (that may result in yellowing of the skin or eyes).
- low number of blood cells known as neutrophils, (sometimes accompanied with fever), red blood cells, white blood cells, lymphocytes, or low number of blood components known as platelets (see section 2); signs and symptoms include developing an infection or fever or bruising easily or getting nose bleeds on a regular basis.
- tumour lysis syndrome (see section 2); this may be associated with a variety of symptoms in the stomach and intestines (for example, nausea, vomiting, diarrhoea), heart (for example, changes in the rhythm), kidney (for example, decreased urine, blood in urine), and nerves and muscles (for example, muscular spasms, weakness, cramps).
- QT interval prolongation (see section 2); signs and symptoms include a change in electrical activity of the heart that can cause serious irregular heart rhythms. Tell your doctor if you have symptoms, such as dizziness, lightheadedness or fainting.

Other side effects may include:

Very common (may affect more than 1 in 10 people):

- Infections
- Reduced number of white blood cells which may result in general weakness and a tendency to develop infections

- Reduced number of lymphocytes (a type of white blood cells) which may result in a tendency to develop infections
- Reduced number of red blood cells which may result in fatigue and shortness of breath
- Decreased appetite
- Headache
- Bleeding
- Pain in the abdomen
- Vomiting
- Diarrhoea
- Nausea
- Mouth inflammation
- Constipation
- Raised bilirubin level which may result in a yellowish colour in the skin, eyes, and other tissues
- Fever
- Chills
- Fatigue
- High levels of liver enzymes (which can be indicators of liver injury) in the blood

Common (may affect up to 1 in 10 people):

- Reduction in the number of various types of blood cells
- Excess of uric acid in the blood
- Excessive accumulation of fluid in the abdomen
- Swelling of the abdomen
- Changes in heart rhythm (may show on electrocardiogram)
- Abnormally high levels of amylase (an enzyme needed for digestion and conversion of starch into sugars) in the blood
- Abnormally high levels of lipase (an enzyme needed to process dietary fat) in the blood
- Hypersensitivity

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below). By reporting side effects, you can help provide more information on the safety of this medicine.

Ireland
HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 676 4971; Fax: +353 1 676 2517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

United Kingdom
Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Malta
ADR Reporting
Website: www.medicinesauthority.gov.mt/adrportal

5. How to store BESPONSA

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

Do not use this medicine after the expiry date which is stated on the vial label and carton after EXP. The expiry date refers to the last day of that month.

Unopened vial

- Store in a refrigerator (2 °C-8 °C).
- Store in the original carton in order to protect from light.
- Do not freeze.

Reconstituted solution

- Use immediately or store in a refrigerator (2 °C-8 °C) for up to 4 hours.
- Protect from light.
- Do not freeze.

Diluted solution

- Use immediately or store at room temperature (20 °C-25 °C) or in a refrigerator (2 °C-8 °C). The maximum time from reconstitution through the end of administration should be ≤ 8 hours, with ≤ 4 hours between reconstitution and dilution.
- Protect from light.
- Do not freeze.

This medicine should be inspected visually for particulate matter and discolouration prior to administration. If particles or discolouration are observed, do not use.

Do not throw away any medicines via wastewater or household waste. Ask your doctor how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What BESPONSA contains

- The active substance is inotuzumab ozogamicin. Each vial contains 1 mg inotuzumab ozogamicin. After reconstitution, 1 mL of solution contains 0.25 mg inotuzumab ozogamicin.
- The other ingredients are sucrose, polysorbate 80, sodium chloride, and tromethamine.

What BESPONSA looks like and contents of the pack

BESPONSA is a powder for concentrate for solution for infusion.

Each pack of BESPONSA contains:

- 1 glass vial containing a white to off-white lyophilised cake or powder.

Marketing Authorisation Holder

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

Manufacturer

Pfizer Ireland Pharmaceuticals

Grange Castle Business Park
Clondalkin
Dublin 22
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Pfizer Limited
Tel: +44 (0) 1304 616161

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Ireland
Pfizer Healthcare Ireland
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This leaflet was last revised in 10/2018

Ref BS 5_0

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only. For full information on dosage and dose modifications please refer to the Summary of Product Characteristics.

Method of administration

BESPONSA is for intravenous use. The infusion must be administered over 1 hour.

Do not administer BESPONSA as an intravenous push or bolus.

BESPONSA must be reconstituted and diluted before administration.

BESPONSA should be administered in 3- to 4-week cycles.

For patients proceeding to a haematopoietic stem cell transplant (HSCT), the recommended duration of treatment is 2 cycles. A third cycle may be considered for those patients who do not achieve a CR/CRi and MRD negativity after 2 cycles. For patients not proceeding to HSCT, a maximum of 6 cycles may be administered. Any patients who do not achieve a CR/CRi within 3 cycles should discontinue treatment (see Summary of Product Characteristics section 4.2).

The table below shows the recommended dosing regimens.

For the first cycle, the recommended total dose for all patients is 1.8 mg/m^2 per cycle, administered as 3 divided doses on Days 1 (0.8 mg/m^2), 8 (0.5 mg/m^2), and 15 (0.5 mg/m^2). Cycle 1 is 3 weeks in duration, but may be extended to 4 weeks if the patient achieves a CR or CRi, and/or to allow recovery from toxicity.

For subsequent cycles, the recommended total dose is 1.5 mg/m^2 per cycle administered as 3 divided doses on Days 1 (0.5 mg/m^2), 8 (0.5 mg/m^2), and 15 (0.5 mg/m^2) for patients who achieve a CR/CRi or 1.8 mg/m^2 per cycle given as 3 divided doses on Days 1 (0.8 mg/m^2), 8 (0.5 mg/m^2), and 15 (0.5 mg/m^2) for patients who do not achieve a CR/CRi. Subsequent cycles are 4 weeks in duration.

Dosing regimen for Cycle 1 and subsequent cycles depending on response to treatment

	Day 1	**Day 8**[a]	**Day 15**[a]
Dosing regimen for Cycle 1			
All patients:			
Dose (mg/m^2)	0.8	0.5	0.5
Cycle length	21 days[b]		
Dosing regimen for subsequent cycles depending on response to treatment			
Patients who have achieved a CR[c] or CRi[d]:			
Dose (mg/m^2)	0.5	0.5	0.5
Cycle length	28 days[e]		
Patients who have not achieved a CR[c] or CRi[d]:			
Dose (mg/m^2)	0.8	0.5	0.5
Cycle length	28 days[e]		

Abbreviations: ANC=absolute neutrophil counts; CR=complete remission; CRi=complete remission with incomplete haematological recovery.

[a] +/- 2 days (maintain a minimum of 6 days between doses).

[b] For patients who achieve a CR/CRi, and/or to allow for recovery from toxicity, the cycle length may be extended up to 28 days (i.e. 7-day treatment-free interval starting on Day 21).

[c] CR is defined as < 5% blasts in the bone marrow and the absence of peripheral blood leukaemic blasts, full recovery of peripheral blood counts (platelets ≥ 100 × 10^9/L and ANC ≥ 1 × 10^9/L) and resolution of any extramedullary disease.

[d] CRi is defined as < 5% blasts in the bone marrow and the absence of peripheral blood leukaemic blasts, incomplete recovery of peripheral blood counts (platelets < 100 × 10^9/L and/or ANC < 1 × 10^9/L) and resolution of any extramedullary disease.

[e] 7-day treatment-free interval starting on Day 21.

Instructions for reconstitution, dilution, and administration

Use appropriate aseptic technique for the reconstitution and dilution procedures. Inotuzumab ozogamicin (which has a density of 1.02 g/mL at 20 °C/68 °F) is light sensitive and should be protected from ultraviolet light during reconstitution, dilution, and administration.

The maximum time from reconstitution through the end of administration should be ≤ 8 hours, with ≤ 4 hours between reconstitution and dilution.

Reconstitution:

- Calculate the dose (mg) and number of vials of BESPONSA required.
- Reconstitute each 1 mg vial with 4 mL of water for injection, to obtain a single-use solution of 0.25 mg/mL of BESPONSA.
- Gently swirl the vial to aid dissolution. Do not shake.
- Inspect the reconstituted solution for particulates and discolouration. The reconstituted solution must be clear to slightly cloudy, colourless, and essentially free of visible foreign matter. If particles or discolouration are observed, do not use.
- BESPONSA contains no bacteriostatic preservatives. The reconstituted solution must be used immediately. If the reconstituted solution cannot be used immediately, it may be stored in a refrigerator (2 °C-8 °C) for up to 4 hours. Protect from light and do not freeze.

Dilution:

- Calculate the required volume of the reconstituted solution needed to obtain the appropriate dose according to patient body surface area. Withdraw this amount from the vial(s) using a syringe. Protect from light. Discard any unused reconstituted solution left in the vial.
- Add the reconstituted solution to an infusion container with sodium chloride 9 mg/mL (0.9%) solution for injection, to a total nominal volume of 50 mL. The final concentration should be between 0.01 and 0.1 mg/mL. Protect from light. An infusion container made of polyvinyl chloride (PVC) (di(2-ethylhexyl)phthalate [DEHP]- or non-DEHP-containing), polyolefin (polypropylene and/or polyethylene), or ethylene vinyl acetate (EVA) is recommended.
- Gently invert the infusion container to mix the diluted solution. Do not shake.
- The diluted solution must be used immediately, stored at room temperature (20 °C-25 °C) or in a refrigerator (2 °C-8 °C). The maximum time from reconstitution through the end of administration should be ≤ 8 hours, with ≤ 4 hours between reconstitution and dilution. Protect from light and do not freeze.

Administration:

- If the diluted solution is stored in a refrigerator (2 °C-8 °C), it must be allowed to equilibrate at room temperature (20 °C-25 °C) for approximately 1 hour prior to administration.
- Filtration of the diluted solution is not required. However, if the diluted solution is filtered, polyethersulphone (PES)-, polyvinylidene fluoride (PVDF)-, or hydrophilic polysulphone (HPS)-based filters are recommended. Do not use filters made of nylon or mixed cellulose ester (MCE).
- Protect the intravenous bag from light using an ultraviolet light-blocking cover (i.e., amber, dark brown, or green bags or aluminium foil) during infusion. The infusion line does not need to be protected from light.
- Infuse the diluted solution for 1 hour at a rate of 50 mL/h at room temperature (20 °C-25 °C). Protect from light. Infusion lines made of PVC (DEHP or non-DEHP-containing), polyolefin (polypropylene and/or polyethylene), or polybutadiene are recommended.

Do not mix BESPONSA or administer as an infusion with other medicinal products.

The storage times and conditions for reconstitution, dilution, and administration of BESPONSA are shown below.

Storage times and conditions for reconstituted and diluted BESPONSA solution

←——Maximum time from reconstitution through the end of administration ≤ 8 hours[a]——→		
Reconstituted solution	**Diluted solution**	
	After start of dilution	**Administration**
Use reconstituted solution immediately or after being stored in a refrigerator (2 °C-8 °C) for up to 4 hours. Protect from light. Do not freeze.	Use diluted solution immediately or after being stored at room temperature (20 °C-25 °C) or in a refrigerator (2 °C-8 °C). The maximum time from reconstitution through the end of administration should be ≤ 8 hours, with ≤ 4 hours between reconstitution and dilution. Protect from light. Do not freeze.	If the diluted solution is stored in a refrigerator (2 °C-8 °C), bring it to room temperature (20 °C-25 °C) for approximately 1 hour prior to administration. Administer diluted solution as a 1-hour infusion at a rate of 50 mL/h at room temperature (20 °C-25 °C). Protect from light.

[a] With ≤ 4 hours between reconstitution and dilution.

Storage conditions and shelf life

Unopened vials

4 years

Reconstituted solution

BESPONSA contains no bacteriostatic preservatives. The reconstituted solution must be used immediately. If the reconstituted solution cannot be used immediately, it may be stored in a refrigerator (2 °C-8 °C) for up to 4 hours. Protect from light and do not freeze.

Diluted solution

The diluted solution must be used immediately or stored at room temperature (20 °C-25 °C) or in a refrigerator (2 °C-8 °C). The maximum time from reconstitution through the end of administration should be ≤ 8 hours, with ≤ 4 hours between reconstitution and dilution. Protect from light and do not freeze.