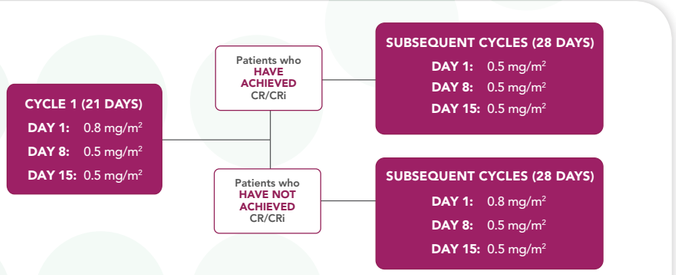
Preventative strategies to consider for VOD/SOS[1,3,4,5]

Preventative measures, that could be considered to help reduce the incidence or severity of VOD/SOS include:

- With reference to the treatment regimen shown in the figure below, an increased number of BESPONSA treatment cycles is associated with an increased incidence of VOD/SOS. For patients planning to receive HSCT, it is recommended that treatment with BESPONSA be limited to 2 cycles; a third cycle could be considered for those patients who do not achieve a complete remission (CR) or complete remission with incomplete haematological recovery (CRi) and a minimal residual disease (MRD) negativity after 2 cycles. For patients not proceeding to HSCT, additional cycles of treatment, up to a maximum of 6 cycles, may be administered. Patients who do not achieve CR/CRi within 3 cycles should discontinue treatment.



Day 8 and 15 doses can be administered ±2 days (maintain minimum of 6 days between doses).
*For patients who achieve a CR or CRi, or to allow for recovery from toxicity, the first cycle length may be extended up to 28 days (i.e. 7-day treatment-free interval starting on Day 21).
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.
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 or ANC <1 × 10^9/L) and resolution of any extramedullary disease.
For subsequent cycles, a 7-day treatment-free interval starting on Day 21 should be observed.
ANC, absolute neutrophil count; CR, complete remission; CRi, complete remission with incomplete haematological recovery of peripheral blood counts.

- Healthcare providers should use their clinical judgment to determine the most appropriate course of therapy for prophylactic treatment of VOD/SOS.
- Use the least hepatotoxic conditioning regimen and, specifically, avoid using regimens that contain 2 alkylating agents.
- When possible, avoid the concomitant use of hepatotoxic drugs peri-transplant.

Additional information

This document does not include complete data for the prescriber. For additional information on the risks discussed on this guide, and other possible risks and side effects of BESPONSA, please refer to the product's leaflet.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Adverse events can be reported directly to the Ministry of Health using the adverse events digital form which is available on the home page of the Ministry of Health website: www.health.gov.il or by this link:
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il
Side effects can also be reported to Pfizer by email:

isr.aereporting@pfizer.com

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This Prescriber Guide, format and content, have been reviewed and approved by the Ministry of Health on July 2018.

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A guide to treatment with

BESPONSA™ inotuzumab ozogamicin INJECTION FOR IV INFUSION

inotuzumab ozogamicin INJECTION FOR INFUSION

Prescribers Guide

BESPONSA is indicated as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (ALL). Adult patients with Philadelphia chromosome positive (Ph+) relapsed or refractory B cell precursor ALL should have failed treatment with at least 1 tyrosine kinase inhibitor (TKI)

BESPONSA treatment is associated with several adverse reactions. This guide provides information mainly on the risk of hepatic veno-occlusive disease/ sinusoidal obstructive syndrome (VOD/SOS). This risk is most marked in patients who undergo subsequent hematopoietic stem cell transplant (HSCT).

Contraindications for BESPONSA[1]

- Hypersensitivity to BESPONSA or any of the other ingredients in this medicine (sucrose, polysorbate 80, sodium chloride, tromethamine)
- Patients who have experienced prior confirmed severe or ongoing VOD/SOS
- Patients with serious ongoing hepatic liver disease (e.g., cirrhosis, nodular regenerative hyperplasia, active hepatitis)

Diagnosis of VOD/SOS[2]

VOD/SOS may be difficult to diagnose. The EBMT criteria for VOD/SOS diagnosis in adults are:

Classical VOD/SOS (in the first 21 days after HSCT)	Late onset VOD/SOS (>21 days after HSCT)
• Bilirubin ≥2 mg/dL and two of the following criteria must be present: – Painful hepatomegaly – Weight gain >5% – Ascites	• Classical VOD/SOS beyond day 21 **OR** • Histologically proven VOD/SOS **OR** • Two or more of the following criteria must be present: – Bilirubin ≥2 mg/dL (or 34 µmol/L) – Painful hepatomegaly – Weight gain >5% **AND** – Haemodynamic or ultrasound evidence of VOD/SOS

These symptoms/signs should not be attributable to other causes.
HSCT, haematopoietic stem cell transplantation; VOD/SOS, veno-occlusive disease/sinusoidal obstructive syndrome.

Risk factors to consider for VOD/SOS[1]

Risk factors that appear to be associated with an increased risk of VOD/SOS include:

- HSCT after BESPONSA treatment
- HSCT conditioning regimen containing 2 alkylating agents
- Serum bilirubin greater than or equal to the upper limit of normal (ULN) prior to HSCT
- Prior HSCT before BESPONSA treatment
- Increased age (eg, ≥ 55 years)
- Ongoing or prior liver disease before BESPONSA treatment
- Later salvage lines
- Greater number of BESPONSA treatment cycles

Monitoring[1]

- Signs and symptoms of VOD/SOS should be monitored closely in all patients, especially post HSCT.
- Signs may include elevations in total bilirubin, hepatomegaly (which may be painful), rapid weight gain, and ascites. Monitoring only total bilirubin may not identify all patients at risk of VOD/SOS.
- In all patients, liver tests should be monitored, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and alkaline phosphatase, prior to and following each dose of BESPONSA.
- For patients who develop abnormal liver tests, liver tests and clinical signs and symptoms of hepatotoxicity should be monitored more frequently.
- For patients who proceed to hematopoietic stem cell transplant (HSCT), liver tests should be monitored closely during the first month post-HSCT, then less frequently thereafter, according to standard medical practice.

Dose modifications for liver test elevations[1]

Elevation of liver tests may require dosing interruption, dose reduction, or permanent discontinuation of BESPONSA .

- For VOD/SOS or other severe liver toxicity, permanently discontinue treatment
- No adjustment to the starting dose is required in patients with hepatic impairment defined by total bilirubin ≤1.5 × upper limit of normal (ULN) and AST/ALT ≤2.5 × ULN.
- Interrupt dosing until recovery of total bilirubin to ≤1.5 × ULN and AST/ALT to ≤2.5 × ULN prior to each dose unless due to Gilbert's syndrome or haemolysis.
- Permanently discontinue treatment if total bilirubin does not recover to ≤1.5 × ULN or AST/ALT does not recover to ≤2.5 × ULN.