PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrBESPONSA™

inotuzumab ozogamicin for injection

Lyophilized powder for solution for infusion
0.9 mg single-dose vial

Anti-neoplastic Agent

Pfizer Canada Inc.
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Kirkland, Quebec
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™ Pfizer Inc.
Pfizer Canada Inc., Licensee

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[Pr]BESPONSA™

inotuzumab ozogamicin for injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	Lyophilized powder for solution for infusion / 0.9 mg	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

Inotuzumab ozogamicin is a CD22-directed antibody-drug conjugate (ADC) consisting of 3 components: 1) the recombinant humanized immunoglobulin class G subtype (IgG4) kappa antibody inotuzumab, specific for human CD22, 2) N-acetyl-gamma-calicheamicin that causes DNA double strand-breaks, and 3) an acid-cleavable linker composed of the condensation product of 4-(4'-acetylphenoxy)-butanoic acid (AcBut) and 3-methyl-3-mercaptobutane hydrazide (known as dimethylhydrazide) that covalently attaches N-acetyl-gamma-calicheamicin to inotuzumab.

INDICATIONS AND CLINICAL USE

BESPONSA (inotuzumab ozogamicin for injection) is indicated as a:

- Monotherapy for the treatment of adults with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukemia (ALL).

Geriatrics (> 65 years of age): In a randomized clinical study of BESPONSA for the treatment of patients with ALL (Study 1), 30/164 (18%) patients treated with BESPONSA were ≥65 years of age. No overall differences were observed in the safety and efficacy of BESPONSA between patients who were <65 and ≥65 years of age. However, increased age was associated with an increased risk of venoocclusive disease/sinusoidal obstruction syndrome (VOD/SOS) after hematopoietic stem cell transplant (HSCT) (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreas,** Hepatotoxicity, including VOD/SOS).

Pediatrics (< 18 years of age): The safety and efficacy of BESPONSA in the pediatric population (<18 years) have not been established

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

Serious Warnings and Precautions

- Post-hematopoietic stem cell transplant (HSCT) non-relapse mortality (see **WARNINGS AND PRECAUTIONS**, **General,** Post HSCT non-relapse mortality)
- Hepatotoxicity, including venoocclusive disease/sinusoidal obstruction syndrome (VOD/SOS) which may be severe, life-threatening or fatal, has been observed in patients receiving BESPONSA (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreas,** Hepatotoxicity, including VOD/SOS)
- Myelosuppression/cytopenias, and complications including infections and bleeding/hemorrhagic events, which may be severe, life-threatening or fatal, were reported in patients receiving BESPONSA (see **WARNINGS AND PRECAUTIONS, Hematologic,** Myelosuppression/cytopenias)
- Tumor lysis syndrome (TLS), which may be severe, life-threatening or fatal, has been observed in patients receiving BESPONSA (see **WARNINGS AND PRECAUTIONS**, **General**, Tumor lysis syndrome).
- Infusion-related reactions (see **WARNINGS AND PRECAUTIONS, General,** Infusion-related reactions)
- QT interval prolongation (see **WARNINGS AND PRECAUTIONS, Cardiovascular,** QT interval prolongation; **DRUG INTERACTIONS,** QTc interval-prolonging drugs; **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacodynamics,** Cardiac electrophysiology)

WARNINGS AND PRECAUTIONS

General

Infusion-related reactions

In the pivotal ALL study (B1931022), infusion-related reactions, all of which were Grade ≤2 in severity, were reported in 4/164 (2%) patients (see **ADVERSE REACTIONS**). Infusion-related reactions generally occurred in Cycle 1 shortly after the end of the BESPONSA infusion and resolved spontaneously or with medical management. Premedication, with a corticosteroid, antipyretic, and antihistamine, is recommended prior to dosing in all patients (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**).

Monitor patients closely during and for at least 1 hour after the end of infusion for the potential onset of infusion-related reactions, including symptoms such as fever, chills, rash or breathing problems. If an infusion-related reaction occurs, interrupt the infusion and institute appropriate

medical management. Depending on the severity of the infusion-related reaction, consider discontinuation of the infusion and/or administration of steroids and antihistamines. For severe or life-threatening infusion reactions, permanently discontinue BESPONSA (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**).

Post-HSCT non-relapse mortality

In the pivotal ALL study (B1931022), a higher post-HSCT non-relapse mortality rate was observed in patients receiving BESPONSA compared to the Investigator's choice of chemotherapy arm, resulting in a higher Day 100 post-HSCT mortality rate.

Overall, 79/164 (48%) patients in the inotuzumab ozogamicin arm and 35/162 (22%) patients in the Investigator's choice of chemotherapy arm had a follow-up HSCT. The post-HSCT non-relapse mortality rate was 31/79 (39%) and 8/35 (23%) in the BESPONSA arm compared to the Investigator's choice of chemotherapy arm, respectively.

In the BESPONSA arm, the most common causes of post-HSCT non-relapse mortality included VOD and infections. Five of the 18 VOD/SOS events that occurred post-HSCT were fatal (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreas,** Hepatotoxicity, including VOD/SOS). Six patients had ongoing VOD at time of death and died due to multiorgan failure (MOF) or infection (3 patients died due to MOF, 2 patients died due to infection, and 1 patient died due to MOF and infection).

Monitor closely for toxicities post-HSCT, including signs and symptoms of infection and VOD (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreas,** Hepatotoxicity, including VOD/SOS and **WARNINGS AND PRECAUTIONS, Hematologic,** Myelosuppression/cytopenias).

Tumor lysis syndrome

In the pivotal ALL study (B1931022), tumor lysis syndrome (TLS), which may be life-threatening or fatal, was reported in 4/164 (2%) patients (see **ADVERSE REACTIONS**). Grade 3/4 TLS was reported in 3/164 (2%) patients. TLS occurred shortly after the end of the BESPONSA infusion and resolved with medical management.

Monitor for signs and symptoms of TLS and treat according to standard medical practice.

Effects on ability to drive and use machines

BESPONSA has moderate influence on the ability to drive and use machines. Patients may experience fatigue during treatment with BESPONSA (see **ADVERSE REACTIONS**). Therefore, caution is recommended when driving or operating machines.

Carcinogenesis and Mutagenesis

Inotuzumab ozogamicin is genotoxic (see **PART II - TOXICOLOGY, Genotoxicity**). Formal carcinogenicity studies have not been conducted with inotuzumab ozogamicin (see **PART II - TOXICOLOGY, Carcinogenicity**).

Cardiovascular

QT interval prolongation

BESPONSA is associated with QTc prolongation. In the pivotal ALL study (B1931022), increases in QT interval corrected for heart rate using Fridericia's formula (QTcF) of ≥60 msec from baseline were measured in 4/162 (3%) patients. No patients had QTcF values >500 msec (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacodynamics,** Cardiac electrophysiology). Grade 2 QT prolongation was reported in 9/162 (6%) patients. No Grade ≥3 QT prolongation or events of Torsade de Pointes were reported (see **ADVERSE REACTIONS, ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics,** Cardiac electrophysiology).

QTc prolongation may lead to an increased risk of ventricular arrhythmias including Torsade de Pointes. Torsade de Pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of Torsade de Pointes increases with the magnitude of QTc prolongation produced by the drug. Torsade de Pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, Torsade de Pointes can progress to ventricular fibrillation and sudden cardiac death. BESPONSA should be administered with caution in patients who have a history of or predisposition for QTc prolongation, other risk factors for Torsade de Pointes, or who are taking medicinal products that are known to prolong QT interval, and in patients with electrolyte disturbances (see **DRUG INTERACTIONS, QTc interval-prolonging drugs**). Hypokalemia, hypomagnesemia, and hypocalcemia should be corrected prior to BESPONSA administration.

Risk factors for Torsade de pointes in the general population include, but are not limited to, the following: female gender; age ≥65 years; baseline prolongation of the QT/QTc interval; presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes; family history of sudden cardiac death at <50 years of age; cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, cardiomyopathy, conduction system disease); history of arrhythmias; electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia) or conditions leading to electrolyte disturbances (e.g., persistent vomiting, eating disorders); bradycardia; acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma); diabetes mellitus; and autonomic neuropathy.

When drugs that prolong the QTc interval are prescribed, healthcare professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and

other information relevant to the use of the drug. Patients should be advised to contact their healthcare provider immediately to report any new chest pain or discomfort, changes in heartbeat, palpitations, dizziness, lightheadedness, fainting, or changes in or new use of other medications.

Electrocardiograms (ECGs) and electrolytes should be obtained prior to the start of treatment and periodically monitored during treatment (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacodynamics,** Cardiac electrophysiology, and **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**, Cardiac).

PR interval prolongation

Prolongation of the PR interval of the electrocardiogram was observed in patients treated with BESPONSA (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacodynamics,** Cardiac electrophysiology, and **DRUG INTERACTIONS, *PR interval-Prolonging Drugs*).**

Caution should be observed in patients with pre-existing conduction system abnormalities (e.g., marked first-degree AV block or second- or third-degree AV block) or a history of rhythm disturbances (e.g., tachyarrhythmias).

Hematologic

In the pivotal ALL study (B1931022), some patients received medication to reduce circulating lymphoblasts prior to their first dose (see **DOSAGE AND ADMINISTRATION, Dosing Considerations**).

Myelosuppression/cytopenias

In the pivotal ALL study (B1931022), neutropenia, thrombocytopenia, anemia, leukopenia, febrile neutropenia, lymphopenia, and pancytopenia, some of which were life-threatening, were reported in patients receiving BESPONSA (see **ADVERSE REACTIONS**).

Thrombocytopenia and neutropenia were reported in 83/164 (51%) and 81/164 (49%) patients, respectively. Grade 3 thrombocytopenia and neutropenia were reported in 23/164 (14%) patients and 33/164 (20%) patients, respectively. Grade 4 thrombocytopenia and neutropenia were reported in 46/164 (28%) patients and 45/164 (27%) patients, respectively. Febrile neutropenia, which may be life-threatening, was reported in 43/164 (26%) patients.

Complications associated with neutropenia and thrombocytopenia (including infections and bleeding/hemorrhagic events, respectively) were reported (see **ADVERSE REACTIONS**).

Infections, including serious infections, some of which were life-threatening or fatal, were reported in 79/164 (48%) patients. Fatal infections, including pneumonia, neutropenic sepsis, sepsis, septic shock, and pseudomonal sepsis, were reported in 8/164 (5%) patients. Bacterial, viral, and fungal infections were reported.

Bleeding/hemorrhagic events, mostly mild in severity, were reported in 54/164 (33%) patients. Grade 3/4 bleeding/hemorrhagic events were reported in 8/164 (5%) patients. One Grade 5 bleeding/hemorrhagic event (intra-abdominal hemorrhage) was reported in 1/164 (1%) patient. The most common bleeding event was epistaxis which was reported in 24/139 (15%) patients.

Monitor complete blood counts prior to each dose of BESPONSA and monitor for signs and symptoms of infection during treatment and after HSCT (see **WARNINGS AND PRECAUTIONS, Hematologic,** Myelosuppression/cytopenias; **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests,** Hematologic), bleeding/hemorrhage, or other effects of myelosuppression during treatment with BESPONSA. As appropriate, administer prophylactic anti-infectives, and employ surveillance testing during and after treatment with BESPONSA. Management of patients with severe infection, bleeding/hemorrhage, or other effects of myelosuppression, including severe neutropenia or thrombocytopenia, may require dosing interruption, dose reduction, or permanent discontinuation of BESPONSA (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**).

Hepatic/Biliary/Pancreas

Hepatotoxicity, including VOD/SOS

In the pivotal ALL study (B1931022), hepatotoxicity, including severe, life-threatening, and sometimes fatal hepatic VOD/SOS, and increases in liver tests, were reported in patients receiving BESPONSA (see **ADVERSE REACTIONS**).

VOD/SOS was reported in 23/164 (14%) patients during or following treatment, or following a HSCT after completion of treatment. Grade 3/4 aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin abnormal liver tests occurred in 7/160 (4%), 7/161 (4%), and 8/161 (5%) patients, respectively (see **ADVERSE REACTIONS)**.

Among all 164 patients treated, VOD/SOS was reported in 5/164 (3%) patients during study therapy or in follow-up without an intervening HSCT. Among the 79 patients who proceeded to a subsequent HSCT (8 of whom received additional salvage therapy after treatment with BESPONSA before proceeding to HSCT), VOD/SOS was reported in 18/79 (23%) patients. Five of the 18 VOD/SOS events that occurred post-HSCT were fatal (see **WARNINGS AND PRECAUTIONS, General,** Post-HSCT non-relapse mortality**)**.

VOD/SOS was reported up to 56 days after the last dose during treatment or during follow-up without an intervening HSCT. The median time from HSCT to onset of VOD/SOS was 15 days (range: 3-57 days).

The following patients may be at increased risk for developing VOD/SOS:

- Patients who have experienced prior VOD/SOS or have serious ongoing hepatic liver disease (e.g., cirrhosis, nodular regenerative hyperplasia, active hepatitis) may be at

increased risk for worsening of liver disease, including developing VOD/SOS, following treatment with BESPONSA.

- Patients with prior HSCT may have an associated increased risk of developing VOD/SOS. Of the 5 patients who experienced VOD/SOS during treatment with BESPONSA but without an intervening HSCT, 2 patients had also received a HSCT before BESPONSA treatment. Among patients who proceeded to HSCT, VOD/SOS was reported after the HSCT that followed treatment with BESPONSA in 5/11 (46%) patients who received a HSCT both prior to and after BESPONSA treatment and in 13/68 (19%) patients who only received a HSCT after BESPONSA treatment.

- Patients who proceed to HSCT. The use of HSCT conditioning regimens containing 2 alkylating agents and last total bilirubin level ≥ upper limit of normal (ULN) before follow-up HSCT are significantly associated with an increased risk of VOD/SOS after HSCT.

- Other factors that may also be associated with an increased risk of VOD/SOS after HSCT include increased age, a history of liver disease and/or hepatitis before treatment, later salvage lines, and a greater number of treatment cycles.

Due to the risk of VOD/SOS, especially after HSCT, monitor closely for signs and symptoms of VOD/SOS; these 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, monitor liver tests, 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, more frequent monitoring of liver tests and clinical signs and symptoms of hepatotoxicity is recommended. For patients who proceed to HSCT, monitor liver tests closely during the first month post-HSCT, then less frequently thereafter, according to standard medical practice. Elevation of liver tests may require dosing interruption, dose reduction, or permanent discontinuation of BESPONSA (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**).

Carefully consider the benefit/risk before administering BESPONSA to patients who have experienced prior VOD/SOS or patients with serious ongoing liver disease (e.g., cirrhosis, nodular regenerative hyperplasia, active hepatitis). If these patients are treated with BESPONSA, monitor closely for signs and symptoms of VOD/SOS and permanently discontinue treatment if VOD/SOS occurs (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**).

Particular attention should be paid when administering BESPONSA to patients who are older, have had a prior HSCT, are in later lines of salvage, and/ or have a prior history of liver disease and/or hepatitis. Due to the risk of VOD, patients proceeding to HSCT, the recommended duration of treatment with inotuzumab ozogamicin is 2 cycles; a third cycle should be considered for those patients who do not achieve a CR or CRi and MRD negativity after 2 cycles (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**). If CR

or CRi and MRD negativity is not achieved by cycle 3, BESPONSA treatment should be permanently discontinued. Avoid the use of HSCT conditioning regimens containing 2 alkylating agents.

Permanently discontinue treatment if VOD/SOS occurs (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**).

If severe VOD/SOS occurs, treat according to standard medical practice.

Immune

Immunizations

The safety of immunization with live vaccines during or following BESPONSA therapy has not been studied. Vaccination with live vaccines is not recommended for at least 2 weeks prior to the start of BESPONSA treatment, during treatment, and until recovery of B-lymphocytes following the last treatment cycle.

Special Populations

Women of childbearing potential: BESPONSA can cause embryo-fetal harm when administered to a pregnant woman.

Pregnancy status should be verified in women with childbearing potential prior to initiating BESPONSA. Advise women of childbearing potential to avoid becoming pregnant and to use effective contraception during treatment with BESPONSA and for at least 8 months after the last dose.

Due to the potential for genotoxicity, advise men with female partners of childbearing potential to use effective contraception during treatment with BESPONSA and for at least 5 months after the last dose.

Fertility: Based on nonclinical findings, male and female fertility may be compromised by treatment with BESPONSA (see **Part II – TOXICOLOGY,** Reproduction toxicity). Patients should seek advice for fertility preservation before treatment.

Pregnant Women: There are no data in pregnant women using BESPONSA. Based on the mechanism of action and safety findings in animals, BESPONSA can cause embryo-fetal harm (see **Part II – TOXICOLOGY,** Reproduction toxicity).

Pregnant women, patients becoming pregnant while receiving BESPONSA, or treated male patients as partners of pregnant women should be apprised of the potential hazard to the fetus. Advise women to contact their healthcare provider if they become pregnant or if pregnancy is suspected, during treatment with BESPONSA.

Nursing Women: There is no data on the presence of BESPONSA or its metabolites in human

milk, the effects on the breastfed infant, or the effects on milk production. A risk to the newborn/infant cannot be excluded. Because of the potential for adverse reactions in breastfed infants, women should not breastfeed during treatment with BESPONSA and for at least 2 months after the final dose (see **Part II – TOXICOLOGY, Genotoxicity**).

Pediatrics (< 18 years of age): The safety and efficacy of BESPONSA in the pediatric population (<18 years) have not been established.

Geriatrics (> 65 years of age): No adjustment to the starting dose is required based on age (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**, Geriatrics). However, increased age has been associated with an increased risk of VOD/SOS post-HSCT (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreas,** Hepatotoxicity, including VOD/SOS).

Monitoring and Laboratory Tests:

CD22 Testing
In order to receive BESPONSA, patients must have documented baseline CD22-positive (>0%) leukemic blasts determined by a validated CD22 assay. Assessment for CD22-positive leukemic blasts should have been performed by laboratories with demonstrated proficiency in the specific technology being utilized. In study B1931022, all evaluable patients had B-cell precursor ALL that expressed CD22. The clinical benefit of BESPONSA in patients with CD22-negative precursor B-cell ALL has not been established; therefore, BESPONSA is not recommended for these patients.

Hepatic
In all patients, monitor liver tests prior to and after each dose with BESPONSA. During and after treatment, signs and symptoms of hepatotoxicity, and signs and symptoms of VOD/SOS should be monitored (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreas,** Hepatotoxicity, including VOD/SOS**)**.

Hematologic
Complete blood counts should be monitored prior to each dose and signs and symptoms of infection, bleeding/hemorrhage, or other effects of myelosuppression should be monitored (see **WARNINGS AND PRECAUTIONS, Hematologic,** Myelosuppression/cytopenias).

Infusion-related reactions
Infusion-related reactions should be monitored during the infusion and for at least 1 hour after the end of the infusion (see **WARNINGS AND PRECAUTIONS, General,** Infusion-related reactions).

Hepatobiliary/Pancreatic
Amylase and lipase increases should be monitored. Potential hepatobiliary disease should be evaluated and treated according to standard medical practice.

Tumor Lysis Syndrome
Signs and symptoms of TLS should be monitored (see **WARNINGS AND PRECAUTIONS,**

General, Tumor lysis syndrome).

Cardiac
ECGs and electrolytes should be obtained prior to the start of treatment and periodically monitored during treatment. Increase ECG monitoring frequency in case of concomitant use of BESPONSA with medicinal products known to prolong QT or PR interval or decrease electrolytes or in patients with risk factors for Torsade de Pointes (see **WARNINGS AND PRECAUTIONS, Cardiovascular,** QT interval prolongation, and **WARNINGS AND PRECAUTIONS, Cardiovascular,** PR interval prolongation).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The following adverse reactions, including appropriate management recommendations, are discussed in greater detail under **WARNINGS AND PRECAUTIONS**:

- Post-HSCT non-relapse mortality
- Hepatotoxicity, including VOD/SOS
- Myelosuppression/cytopenias
- Infusion-related reactions
- Tumor lysis syndrome
- QT interval prolongation
- PR interval prolongation

The adverse reactions described in this section reflect exposure to BESPONSA in 164 patients with relapsed or refractory ALL who participated in a randomized clinical study of BESPONSA versus Investigator's choice of chemotherapy (fludarabine + cytarabine + granulocyte colony-stimulating factor [FLAG], mitoxantrone + cytarabine [MXN/Ara-C], or high dose cytarabine [HIDAC]) (Study 1) (see **Part II - CLINICAL TRIALS,** Study design and patient demographics). Of the 164 patients who received BESPONSA, the median age was 47 years (range: 18-78 years), 56% were male, 68% had received 1 prior treatment regimen for ALL, 31% had received 2 prior treatment regimens for ALL, 68% were White, 19% were Asian, and 2% were Black.

In patients who received BESPONSA, the median duration of treatment was 8.9 weeks (range: 0.1-26.4 weeks), with a median of 3 treatment cycles started in each patient. In patients who received Investigator's choice of chemotherapy, the median duration of treatment was 0.9 weeks (range: 0.1-15.6 weeks), with a median of 1 treatment cycle started in each patient.

In patients who received BESPONSA, the most common (≥10%) adverse reactions (frequency not adjusted for exposure duration) were thrombocytopenia, neutropenia, infection, anemia, leukopenia, fatigue, hemorrhage, pyrexia, nausea, headache, febrile neutropenia, transaminases increased, abdominal pain, gamma-glutamyltransferase increased, hyperbilirubinemia, lymphopenia, diarrhea, constipation, vomiting, stomatitis, alkaline phosphatase increased, decreased appetite and chills.

In patients who received BESPONSA, the most common (≥10%) Grade 3/4 adverse reactions were neutropenia, thrombocytopenia, leukopenia, febrile neutropenia, anemia, infection, lymphopenia, and GGT increased.

Deaths (Grade 5 adverse events [frequency not adjusted for exposure duration]) were reported in 26/164 (16%) of patients in the BESPONSA arm and 16/143 (11%) of patients in the Investigator's choice of chemotherapy arm. The most common (≥2 patients) reasons for deaths (Grade 5 adverse events) were disease progression, VOD, pneumonia, and sepsis in the BESPONSA arm and disease progression, respiratory failure, multiorgan failure, and sepsis in the Investigator's choice of chemotherapy arm.

Serious adverse reactions were reported in 39% of patients who received BESPONSA. The most common (≥2%) serious adverse reactions were infection, febrile neutropenia, hemorrhage, abdominal pain, pyrexia, VOD/SOS, and fatigue.

Overall, 26/164 patients (16%) in the BESPONSA arm and 9/143 patients (6%) patients in the Investigator's choice of chemotherapy arm discontinued treatment due to an adverse reaction, 3/164 patients (3%) in the BESPONSA arm and 3/143 patients (2%) patients in the Investigator's choice of chemotherapy arm had a dose reduction due to an adverse reaction, and 69/164 patients (42%) in the BESPONSA arm and 11/143 patients (8%) patients in the Investigator's choice of chemotherapy arm had a dose delay due to an adverse reaction.

In patients who received BESPONSA, the most common (≥2%) adverse reactions reported as the reason for permanent discontinuation were infection (6%), thrombocytopenia (2%), hyperbilirubinemia (2%), transaminases increased (2%), and hemorrhage (2%); the most common (≥5%) adverse reactions reported as the reason for dosing interruption were neutropenia (17%), infection (10%), thrombocytopenia (10%), transaminases increased (6%); and febrile neutropenia (5%), and the most common (≥1%) adverse reactions reported as the reason for dose reduction were neutropenia (1%), thrombocytopenia (1%), and transaminases increased (1%).

VOD was reported in 23/164 (14%) patients and 3/143 (2%) patients who received inotuzumab ozogamicin and Investigator's choice of chemotherapy, respectively, during or following treatment or following a HSCT after completion of treatment (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreas,** Hepatotoxicity, including VOD/SOS).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1 shows the adverse reactions with ≥1% incidence reported in patients with relapsed or refractory ALL who received BESPONSA or Investigator's choice of chemotherapy.

Table 1. Adverse Reactions With ≥1% Incidence[a] in Patients With Relapsed or Refractory B-Cell Precursor ALL Who Received BESPONSA or Investigator's Choice of Chemotherapy (FLAG, MXN/Ara-C, or HIDAC)

System Organ Class Adverse Reaction	BESPONSA (N=164)		FLAG, MXN/Ara-C, or HIDAC (N=143[b])	
	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Infections and infestations				
Infection[c]	48	28	76	54
Blood and lymphatic system disorders				
Thrombocytopenia[d]	51	42	61	59
Neutropenia[e]	49	48	45	43
Anemia[f]	36	24	59	47
Leukopenia[g]	35	33	43	42
Febrile neutropenia	26	26	53	53
Lymphopenia[h]	18	16	27	26
Pancytopenia[i]	2	1	7	5
Metabolism and nutrition disorders				
Decreased appetite	12	1	13	2
Hyperuricemia	4	2	1	0
Tumor lysis syndrome	2	2	3	1
Nervous system disorders				
Headache[j]	28	2	27	1
Vascular disorders				
Hemorrhage[k]	33	5	28	5
Gastrointestinal disorders				
Nausea	31	2	46	0
Abdominal pain[l]	23	3	23	1
Diarrhea	17	1	38	1
Constipation	16	0	24	0
Vomiting	15	1	24	0
Stomatitis[m]	13	2	26	3
Abdominal distention	6	0	1	0
Ascites	4	2	0	0
Hepatobiliary disorders				
Hyperbilirubinemia	21	5	17	6
Venoocclusive liver disease[n]	3	2	0	0
General disorders and administration site conditions				
Fatigue[o]	35	5	25	3
Pyrexia	32	3	42	6
Chills	11	0	11	0
Investigations				
Transaminases increased[p]	26	7	13	5

Table 1. Adverse Reactions With ≥1% Incidence[a] in Patients With Relapsed or Refractory B-Cell Precursor ALL Who Received BESPONSA or Investigator's Choice of Chemotherapy (FLAG, MXN/Ara-C, or HIDAC)

System Organ Class Adverse Reaction	BESPONSA (N=164)		FLAG, MXN/Ara-C, or HIDAC (N=143[b])	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	%	%	%	%
Gamma-glutamyltransferase increased	21	10	8	4
Alkaline phosphatase increased	13	2	7	0
Lipase increased	9	4	1	1
Amylase increased	5	2	1	0
Electrocardiogram QT prolonged	1	0	1	0
Injury, poisoning and procedural complications				
Infusion-related reaction[q]	2	0	1	0

Adverse reactions included treatment-emergent all-causality events that commenced on or after Cycle 1 Day 1 within 42 days after the last dose of BESPONSA, but prior to the start of a new anticancer treatment (including HSCT).

Preferred terms were retrieved by applying the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.

Abbreviations: ALL=acute lymphoblastic leukemia; FLAG=fludarabine + cytarabine + granulocyte colony-stimulating factor; HIDAC=high dose cytarabine; HSCT=hematopoietic stem cell transplant; MXN/Ara-C=mitoxantrone + cytarabine; N=number of patients; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events, VOD/SOS=venoocclusive liver disease/sinusoidal obstruction syndrome.

[a] Only adverse reactions with ≥10% incidence in the BESPONSA arm are included.

[b] 19 patients randomized to FLAG, MXN/Ara-C, or HIDAC did not receive treatment.

[c] Infection includes any reported preferred terms for BESPONSA retrieved in the System Organ Class Infections and infestations.

[d] Thrombocytopenia includes the following reported preferred terms: Platelet count decreased and Thrombocytopenia.

[e] Neutropenia includes the following reported preferred terms: Neutropenia and Neutrophil count decreased.

[f] Anemia includes the following reported preferred terms: Anemia and Hemoglobin decreased.

[g] Leukopenia includes the following reported preferred terms: Leukopenia, Monocytopenia, and White blood cell count decreased.

[h] Lymphopenia includes the following reported preferred terms: B-lymphocyte count decreased, Lymphocyte count decreased, and Lymphopenia.

[i] Pancytopenia includes the following reported preferred terms: Bone marrow failure, Febrile bone marrow aplasia, and Pancytopenia.

[j] Headache includes the following reported preferred terms: Headache, Migraine, and Sinus headache.

[k] Hemorrhage includes reported preferred terms for BESPONSA retrieved in the Standard MedDRA Query (narrow) for Hemorrhage terms (excluding laboratory terms), resulting in the following preferred terms: Conjunctival hemorrhage, Contusion, Ecchymosis, Epistaxis, Eyelid bleeding, Gastrointestinal hemorrhage, Gingival bleeding, Gastritis hemorrhagic, Hematemesis, Hematochezia, Hematotympanum, Hematuria, Hemorrhoidal hemorrhage, Hemorrhage intracranial, Hemorrhage subcutaneous, Intra-abdominal hemorrhage, Lip hemorrhage, Lower gastrointestinal hemorrhage, Mesenteric hemorrhage, Metrorrhagia, Mouth hemorrhage, Muscle hemorrhage, Oral mucosa hematoma, Petechiae, Post-procedural hematoma, Rectal hemorrhage, Shock hemorrhagic, Subcutaneous hematoma, Subdural hematoma, Upper gastrointestinal hemorrhage, and Vaginal hemorrhage.

[l] Abdominal pain includes the following reported preferred terms: Abdominal pain, Abdominal pain lower,

Table 1. Adverse Reactions With ≥1% Incidence[a] in Patients With Relapsed or Refractory B-Cell Precursor ALL Who Received BESPONSA or Investigator's Choice of Chemotherapy (FLAG, MXN/Ara-C, or HIDAC)

System Organ Class Adverse Reaction	BESPONSA (N=164)		FLAG, MXN/Ara-C, or HIDAC (N=143[b])	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	%	%	%	%

Abdominal pain upper, Abdominal tenderness, Esophageal pain, and Hepatic pain.

[m] Stomatitis includes the following reported preferred terms: Aphthous ulcer, Mucosal inflammation, Mouth ulceration, Oral pain, Oropharyngeal pain, and Stomatitis.

[n] In the BESPONSA arm, VOD/SOS includes 1 additional patient with Venoocclusive liver disease that occurred at Day 56 with no intervening HSCT.

[o] Fatigue includes the following reported preferred terms: Asthenia and Fatigue.

[p] Transaminases increased includes the following reported preferred terms: Aspartate aminotransferase increased, Alanine aminotransferase increased, Hepatocellular injury, and Hypertransaminasemia.

[q] Infusion-related reaction includes the following reported preferred terms: Hypersensitivity and Infusion-related reaction

Abnormal Hematologic and Clinical Chemistry Findings

Table 2 shows the clinically important laboratory abnormalities reported in patients with relapsed or refractory ALL who received BESPONSA or Investigator's choice of chemotherapy.

Table 2. Laboratory Abnormalities in Patients With Relapsed or Refractory B-Cell Precursor ALL Who Received BESPONSA or Investigator's Choice of Chemotherapy (FLAG, MXN/Ara-C, or HIDAC)

Laboratory Abnormality	BESPONSA			FLAG, MXN/Ara-C, or HIDAC		
		All Grades	Grade 3/4		All Grades	Grade 3/4
	N	%	%	N	%	%
Hematology						
Platelet count decreased	161	98	76	142	100	99
Hemoglobin decreased	161	94	40	142	100	70
Leukocytes decreased	161	95	82	142	99	98
Neutrophil count decreased	160	94	86	130	93	88
Lymphocytes (absolute) decreased	160	93	71	127	97	91
Chemistry						
GGT increased	148	67	18	111	68	17
AST increased	160	71	4	134	38	4
ALP increased	158	57	1	133	52	3
ALT increased	161	49	4	137	46	4
Blood bilirubin increased	161	36	5	138	35	6
Lipase increased	139	32	13	90	20	2
Hyperuricemia	158	16	3	122	11	0
Amylase increased	143	15	2	102	9	1

Abbreviations: ALL=acute lymphoblastic leukemia; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; FLAG=fludarabine + cytarabine + granulocyte colony-stimulating factor; GGT=gamma-glutamyltransferase; HIDAC=high dose cytarabine; MXN/Ara-C=mitoxantrone + cytarabine; N=number of patients.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity.

In clinical studies of BESPONSA in patients with relapsed or refractory ALL, the immunogenicity of BESPONSA was evaluated using an electrochemiluminescence (ECL)-based immunoassay to test for anti-inotuzumab ozogamicin antibodies. For patients whose sera tested positive for anti-inotuzumab ozogamicin antibodies, a cell-based luminescence assay was performed to detect neutralizing antibodies.

In clinical studies of BESPONSA in patients with relapsed or refractory ALL, 7/236 (3%) patients tested positive for anti-inotuzumab ozogamicin antibodies. No patients tested positive for neutralizing anti-inotuzumab ozogamicin antibodies. In patients who tested positive for anti-inotuzumab ozogamicin antibodies, the presence of anti-inotuzumab ozogamicin antibodies did not affect clearance following BESPONSA treatment. The number of patients was too small to assess the impact of anti-inotuzumab ozogamicin antibodies on efficacy and safety.

DRUG INTERACTIONS

No clinical drug interaction studies have been performed with BESPONSA (see **ACTION AND CLINICAL PHARMACOLOGY, Drug Interactions**).

QTc Interval-Prolonging Drugs: In a randomized clinical study of BESPONSA in patients with relapsed or refractory ALL (Study 1), prolongation of the QTc interval was observed with inotuzumab ozogamicin (see **WARNINGS AND PRECAUTIONS**, **Cardiovascular,** QT interval prolongation, and **ADVERSE REACTIONS**). The concomitant use of BESPONSA with medicinal products known to prolong QT interval or able to induce Torsade de Pointes may increase the risk of clinically significant QTc prolongation. While the patient is using BESPONSA, other QTc-prolonging drugs should be discontinued and alternative concomitant drugs chosen that do not prolong the QTc interval. When it is not feasible to avoid concomitant use of drugs known to prolong QTc interval, obtain ECGs and electrolytes prior to the start of treatment, after initiation of any drug known to prolong the QTc, and periodically monitor as clinically indicated during treatment (see **WARNINGS AND PRECAUTIONS, Cardiovascular,** QT interval prolongation).

***PR Interval-Prolonging Drugs*:** Prolongation of the PR interval of the electrocardiogram was observed in patients treated with BESPONSA (see **WARNINGS AND PRECAUTIONS, Cardiovascular,** PR interval prolongation, and **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacodynamics,** Cardiac electrophysiology). Co-administration of BESPONSA with other drugs that cause PR interval prolongation should be undertaken with caution.

Drugs that Affect Electrolytes: Use of BESPONSA with drugs that can decrease electrolyte levels should be avoided to the extent possible.

Current information sources should be consulted for newly approved drugs that prolong the QTc or PR interval or decrease electrolytes, as well as for older drugs for which these effects have been established.

Drug-Food Interactions

No formal drug-food interaction studies have been conducted with BESPONSA.

Drug-Herb Interactions

No formal drug-herb interaction studies have been conducted with BESPONSA.

Drug-Laboratory Interactions

No formal drug-laboratory interaction studies have been conducted with BESPONSA.

Drug-Lifestyle Interactions

No formal drug-lifestyle interaction studies have been conducted with BESPONSA.

DOSAGE AND ADMINISTRATION
Dosing Considerations

- For patients with circulating lymphoblasts, cytoreduction with a combination of hydroxyurea, steroids, and/or vincristine to a peripheral blast count ≤10,000/mm^3 is recommended prior to the first dose.

- Premedication with a corticosteroid, antipyretic, and antihistamine is recommended prior to dosing (see **DOSAGE AND ADMINISTRATION, Dosing Considerations**). Patients should be observed during and for at least 1 hour after the end of infusion for symptoms of infusion-related reactions (see **DOSAGE AND ADMINISTRATION, Dosing Considerations, and WARNINGS AND PRECAUTIONS, General,** Infusion-related reactions).

- BESPONSA must be reconstituted and diluted before administration. For instructions on reconstitution and dilution of the medicinal product before administration, see **DOSAGE AND ADMINISTRATION, Instructions for Reconstitution, Dilution, and Administration.**

Recommended Dose and Dosage Adjustment

Administer BESPONSA intravenously by infusion over 1 hour. Do not administer BESPONSA as an intravenous push or bolus.

Administer BESPONSA in 3- to 4-week cycles. For patients proceeding to HSCT, the recommended duration of treatment with BESPONSA is 2 cycles. A third cycle should be considered for those patients who do not achieve a CR or a CRi and MRD negativity after 2 cycles (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreas,** Hepatotoxicity, including VOD/SOS). For patients with a CR or CRi and MRD negativity not proceeding to HSCT, a maximum of 6 cycles may be administered.

Any patients who do not achieve a CR or CRi within 3 cycles should discontinue treatment.

Table 3 shows the recommended dosing regimens.

For the first cycle, the recommended total dose of BESPONSA 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 a CRi, and/or to allow recovery from toxicity.

For subsequent cycles, the recommended total dose of BESPONSA 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 or 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 or CRi. Subsequent cycles are 4 weeks in duration.

Table 3. 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)[b]	0.8	0.5	0.5
Cycle length	21 days[c]		
Dosing regimen for subsequent cycles depending on response to treatment			
Patients who have achieved a CR[c] or CRi[d]:			
Dose (mg/m^2)[b]	0.5	0.5	0.5
Cycle length	28 days[f]		
Patients who have not achieved a CR[d] or CRi[e]:			
Dose (mg/m^2)[b]	0.8	0.5	0.5
Cycle length	28 days[f]		

Abbreviations: CR= complete remission; CRi= complete remission with incomplete hematologic recovery.

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

[b] Dose is based on the patient's body surface area (m^2).

[c] For patients who achieve a CR or a CRi, 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).

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

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

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

Dose Modification

Dose modification of BESPONSA may be required based on individual safety and tolerability (see **WARNINGS AND PRECAUTIONS**). Management of some adverse drug reactions may require dosing interruptions and/or dose reductions, or permanent discontinuation of BESPONSA (see **WARNINGS AND PRECAUTIONS**, and **ADVERSE REACTIONS**). If the dose is reduced due to BESPONSA-related toxicity, the dose must not be re-escalated.

Table 4 and Table 5 show the dose modification guidelines for hematologic and non-hematologic toxicities, respectively. BESPONSA doses within a treatment cycle (i.e., Days 8 and/or 15) do not need to be interrupted due to neutropenia or thrombocytopenia, but dosing interruptions within a cycle are recommended for non-hematologic toxicities.

Table 4. Dose Modifications for Hematologic Toxicities

Hematologic toxicity	Dose modification(s)
If prior to BESPONSA treatment:	
ANC was ≥1 x 10^9/L	If ANC decreases, then interrupt the next cycle of treatment until recovery of ANC to ≥1 x 10^9/L.
Platelet count was ≥50 x 10^9/L[a]	If platelet count decreases, then interrupt the next cycle

Table 4. Dose Modifications for Hematologic Toxicities

Hematologic toxicity	Dose modification(s)
	of treatment until platelet count recovers to ≥50 x 10^9/L[a].
ANC was <1 x 10^9/L and/or platelet count was <50 x 10^9/L[a]	If ANC and/or platelet count decreases, then interrupt the next cycle of treatment until at least one of the following occurs: - ANC and platelet count recover to at least baseline levels for the prior cycle, or - ANC recovers to ≥1 x 10^9/L and platelet count recovers to ≥50 x 10^9/L[a], or - Stable or improved disease (based on most recent bone marrow assessment) and the ANC and platelet count decrease is considered to be due to the underlying disease (not considered to be BESPONSA-related toxicity).

Abbreviation: ANC= absolute neutrophil count.
[a] Platelet count used for dosing should be independent of blood transfusion.

Table 5. Dose Modifications for Non-hematologic Toxicities

Non-hematologic toxicity	Dose modification(s)
VOD/SOS or other severe liver toxicity	Permanently discontinue treatment (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic,** Hepatotoxicity, including VOD/SOS).
Total bilirubin >1.5 x ULN and AST/ALT >2.5 x ULN	Interrupt the dosing until recovery of total bilirubin to ≤1.5 x ULN and AST/ALT to ≤2.5 x ULN prior to each dose unless due to Gilbert's syndrome or hemolysis. Permanently discontinue treatment if total bilirubin does not recover to ≤1.5 x ULN or AST/ALT does not recover to ≤2.5 x ULN (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic,** Hepatotoxicity, including VOD/SOS).
Infusion-related reaction	Interrupt the infusion and institute appropriate medical management. Depending on the severity of the infusion-related reaction, consider discontinuation of the infusion or administration of steroids and antihistamines. For severe or life-threatening infusion reactions, permanently discontinue treatment (see **WARNINGS AND PRECAUTIONS, General,** Infusions-related reaction).
Non-hematologic toxicity ≥Grade 2[a]	Interrupt treatment until recovery to Grade 1 or pre-treatment grade levels prior to each dose.

Abbreviations: ALT= alanine aminotransferase; AST= aspartate aminotransferase; VOD/SOS= venoocclusive liver disease/sinusoidal obstruction syndrome; ULN= upper limit of normal.
[a] Severity grade according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0

Table 6 shows the dose modification guidelines depending on the duration of dosing interruptions due to toxicity.

Table 6. Dose Modifications Depending on Duration of Dosing Interruption Due to Toxicity

Duration of dosing interruption due to toxicity	Dose modification(s)
<7 days (within a cycle)	Interrupt next dose (maintain a minimum of 6 days between doses).
≥7 days	Omit next dose within the cycle.
≥14 days	Once adequate recovery is achieved, decrease the total dose by 25% for the subsequent cycle. If further dose modification is required, then reduce the number of doses to 2 per cycle for subsequent cycles. If a 25% decrease in the total dose followed by a decrease to 2 doses per cycle is not tolerated, then permanently discontinue treatment.
>28 days	Consider permanent discontinuation of treatment.

Special Populations and Conditions

Pediatrics (< 18 years of age): The safety and efficacy of BESPONSA in the pediatric population have not been established.

Geriatrics (> 65 years of age): Based on a population pharmacokinetic analysis of pooled data in 765 patients with relapsed or refractory ALL [n=234] and relapsed or refractory non-Hodgkin lymphoma (NHL) [n=531] (range: 18-92 years; n=314 ≥65 years), the effect of age on clearance and volume of distribution was not significant. No adjustment to the starting dose is required based on age (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, Geriatrics).

Hepatic Impairment: No formal studies of inotuzumab ozogamicin in patients with hepatic impairment have been conducted.

No adjustment to the starting dose is required when administering BESPONSA to patients with hepatic impairment defined by total bilirubin ≤1.5 × ULN and AST/ALT ≤2.5 × ULN (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**, Hepatic insufficiency).

There is limited safety information available in patients with hepatic impairment defined by total bilirubin >1.5 × ULN and AST/ALT >2.5 × ULN prior to dosing. 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 hemolysis. Permanently discontinue treatment if total bilirubin does not recover to ≤1.5 × ULN or AST/ALT does not recover to ≤2.5 × ULN (see Table 5; **ACTION AND CLINICAL PHARMACOLOGY,** Special Populations and Conditions***).***

Renal Impairment: No formal studies of inotuzumab ozogamicin in patients with renal impairment have been conducted.

No adjustment to the starting dose is required when administering BESPONSA to patients with mild or moderate renal impairment (creatinine clearance [CrCL] 60-89 mL/min or 30-59 mL/min respectively) (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions,** Renal insufficiency).

There is limited data available on the safety and efficacy of inotuzumab ozogamicin in patients with severe renal impairment (CrCL 15-29 mL/min). Based on a population pharmacokinetic analysis, which included 4 patients with severe renal impairment who received no adjustment to the starting dose, the clearance of inotuzumab ozogamicin was similar to patients with normal renal function. However, given the limited information on inotuzumab ozogamicin in patients with severe renal impairment (n=4), interpretation of the data should be made with caution.

The safety and efficacy of inotuzumab ozogamicin have not been studied in patients with end stage renal disease.

Instructions for Reconstitution, Dilution, and Administration

Use appropriate aseptic technique for the reconstitution and dilution procedures. BESPONSA (which has a density of 1.02 g/mL at 20°C) 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 vial with 4 mL of Sterile Water for Injection, USP, to obtain a concentration of 0.25 mg/mL of BESPONSA that delivers 3.6 mL (0.9 mg).
- Gently swirl the vial to aid dissolution. **Do not shake**.
- Inspect the reconstituted solution for particulates and discoloration. The reconstituted solution should be clear to slightly cloudy, colorless, and essentially free of visible foreign matter.
- BESPONSA contains no bacteriostatic preservatives. The reconstituted solution should be used immediately. If the reconstituted solution cannot be used immediately, it may be refrigerated (2-8°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 0.9% Sodium Chloride for Injection, USP, 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 should be used immediately or stored at room temperature (20-25°C) or refrigerated (2-8°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 refrigerated (2-8°C), the solution should be allowed to equilibrate at room temperature (20-25°C) for approximately 1 hour prior to administration. **Protect from light.**
- Filtration of the diluted solution is not required. However, if the diluted solution is filtered, polyethersulfone (PES)-, polyvinylidene fluoride (PVDF)- or hydrophilic polysulfone (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 aluminum 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/hour at room temperature (20-25°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.

See Table 7 under **STORAGE AND STABILITY** for the storage times and conditions for reconstitution, dilution, and administration of BESPONSA.

Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

OVERDOSAGE

There is no specific treatment or antidote for inotuzumab ozogamicin overdose. Treatment of inotuzumab ozogamicin overdose should consist of general supportive measures.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Inotuzumab ozogamicin is a CD22-directed ADC. Inotuzumab is a humanized IgG4 antibody which specifically recognizes human CD22. The small molecule, N-acetyl-gamma-calicheamicin, is a cytotoxic semisynthetic natural product. N-acetyl-gamma-calicheamicin is covalently attached to the antibody via a linker composed of the condensation product of 4-(4'-acetylphenoxy)-butanoic acid (AcBut) and 3-methyl-3-mercaptobutane hydrazide (known as dimethylhydrazide). Nonclinical data suggest that the anticancer activity of inotuzumab ozogamicin is due to the binding of the ADC to CD22-expressing tumor cells, followed by internalization of the ADC-CD22 complex, and the intracellular release of N-acetyl-gamma-calicheamicin dimethylhydrazide via hydrolytic cleavage of the linker. N-acetyl-gamma-calicheamicin dimethylhydrazide induces double-stranded DNA breaks, subsequently inducing cell cycle arrest and apoptotic cell death.

Pharmacodynamics

During the treatment period, the pharmacodynamic response to inotuzumab ozogamicin was characterized by the depletion of CD22-positive leukemic blasts.

Cardiac electrophysiology

In a randomized clinical study in patients with relapsed or refractory ALL (Study B1931022), the mean change from baseline QTcF interval was 4.4 ms (90% CI 2.7, 6.1; n=159) and 1.3 ms (90% CI -0.9, 3.5; n=103) on Cycle 1/Day 1, 5.6 ms (90% CI 2.9, 8.4; N=121) and 12.6 msec (on Cycle 2/Day 1; N=23), and 15.3 ms (90% CI 9.5, 21.1; N=41) and 25 msec (90% CI 25,25; N=1) on Cycle 4/Day 1 in the BESPONSA arm and Investigator's choice of chemotherapy arm, respectively. Increases in QTcF of ≥60 msec from baseline were measured in 4/162 patients (3%) in the BESPONSA arm and 3/124 (2%) patients in the Investigator's choice of chemotherapy arm. One subject (0.6%) in the BESPONSA arm had a treatment-emergent maximum QTcF interval >480 ms. QTcF values >500 ms were not observed in the BESPONSA arm.

The mean change from baseline PR interval was -0.6 ms (90% CI -1.7, 0.5; N=158) and -0.7 ms (90% CI -2.1, 0.6; N=103) on Cycle 1/Day 1, 4.9 ms (90% CI 3.1, 6.8; N=120) and 5.1 ms (90% CI 1.0, 9.2; N=23) on Cycle 2/Day 1 (N=120), and 7.8 ms (90% CI 4.0, 11.5; N=44) and 43.3 ms (90% CI 43.3,43.3; N=1) on Cycle 4/Day 1 in the BESPONSA arm and Investigator's choice of chemotherapy arm, respectively. The proportion of subjects with on-treatment PR values >200 ms was 10/162 (6.2%) in the inotuzumab ozogamicin BESPONSA arm and 1/125 (0.8%) in the Investigator's choice of chemotherapy arm.

Pharmacokinetics

The pharmacokinetics of inotuzumab ozogamicin was evaluated in preliminary clinical trials and in a population pharmacokinetic analysis of pooled data in 765 patients with relapsed or refractory ALL and non-Hodgkin lymphoma (NHL). The pooled data used for the population

pharmacokinetic analysis was from two (2) studies in adult patients with relapsed or refractory ALL (n=234) and 9 studies in adult patients with relapsed or refractory NHL (n=531). In studies with patients with ALL, inotuzumab ozogamicin was administered as a single-agent, and in the studies with patients with NHL, inotuzumab ozogamicin was administered as a single-agent, in combination with rituximab, or in combination with rituximab plus chemotherapy.

In patients with relapsed or refractory ALL, steady-state exposure was achieved by Cycle 4. The mean maximum concentration (C_{max}) of inotuzumab ozogamicin was 308 ng/mL. Based on the population pharmacokinetic analysis, the mean simulated total AUC per cycle was 100,000 ng·hr/mL.

Distribution: In vitro, the binding of N-acetyl-gamma-calicheamicin dimethylhydrazide to human plasma proteins is approximately 97%.

Based on the population pharmacokinetic analysis, the total volume of distribution of inotuzumab ozogamicin was approximately 12 L.

Metabolism: In vitro, N-acetyl-gamma-calicheamicin dimethylhydrazide was primarily metabolized via nonenzymatic reduction. In vitro, N-acetyl-gamma-calicheamicin dimethylhydrazide is a substrate of P-glycoprotein (P-gp). In humans, N-acetyl-gamma-calicheamicin dimethylhydrazide serum levels were typically below the limit of quantitation.

Elimination: Based on the population pharmacokinetic analysis, inotuzumab ozogamicin pharmacokinetics were well characterized by a 2-compartment model with linear and time-dependent clearance components. In 234 patients with relapsed or refractory ALL, the estimated clearance of inotuzumab ozogamicin at steady state was 0.0333 L/hr and the estimated terminal half-life ($t_{1/2}$) was 12.3 days. Following administration of multiple doses, a 5.3 times accumulation of inotuzumab ozogamicin was predicted by Cycles 4.

Based on a population pharmacokinetic analysis of pooled data in 765 patients with relapsed or refractory ALL (n=234) and NHL (n=531), body surface area was found to significantly affect inotuzumab ozogamicin disposition. The dose of BESPONSA is administered based on body surface area (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**).

Drug Interactions

No formal clinical drug interaction studies have been performed with BESPONSA.

Effect of Other Drugs on BESPONSA

In vitro, N-acetyl-gamma-calicheamicin dimethylhydrazide is a substrate of P-glycoprotein (P-gp).

In vitro, N-acetyl-gamma-calicheamicin dimethylhydrazide is primarily metabolized via nonenzymatic reduction. Therefore, coadministration of BESPONSA with inhibitors or inducers

of cytochrome P450 (CYP) or uridine diphosphate glucuronosyltransferase (UGT) drug metabolizing enzymes are unlikely to alter exposure to N-acetyl-gamma-calicheamicin dimethylhydrazide.

Based on a population pharmacokinetic analysis in 765 patients with relapsed or refractory ALL (n=234) and NHL (n=531), concomitant administration of cytoreductive drugs including hydroxyurea, granulocyte colony-stimulating factors including filgrastim or lenograstim, and P-gp inhibitors, had no apparent effect on inotuzumab ozogamicin clearance.

Effect of BESPONSA on Other Drugs

Effect on CYP substrates
In vitro, N-acetyl-gamma-calicheamicin dimethylhydrazide and inotuzumab ozogamicin had a low potential to inhibit the activities of CYP1A2, CYP2A6 (tested only using inotuzumab ozogamicin), CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 or to induce the activities of CYP1A2, CYP2B6, and CYP3A4 at clinically relevant concentrations.

Effect on UGT substrates
In vitro, N-acetyl-gamma-calicheamicin dimethylhydrazide had a low potential to inhibit the activities of UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 at clinically relevant concentrations.

Effects on drug transporter substrates
In vitro, N-acetyl-gamma-calicheamicin dimethylhydrazide had a low potential to inhibit the activities of P-gp, breast cancer resistance protein (BCRP), organic anion transporter (OAT)1 and OAT3, organic cation transporter (OCT)2, and organic anion transporting polypeptide (OATP)1B1 and OATP1B3 at clinically relevant concentrations.

Special Populations and Conditions

Pediatrics: The safety and efficacy of BESPONSA in the pediatric population (<18 years) have not been established.

Geriatrics: Based on a population pharmacokinetic analysis of pooled data in 765 patients with relapsed or refractory ALL (n=234) and NHL (n=531), age did not significantly affect inotuzumab ozogamicin disposition.

Gender: Based on a population pharmacokinetic analysis of pooled data in 765 patients with relapsed or refractory ALL (n=234) and NHL (n=531), gender did not significantly affect inotuzumab ozogamicin disposition.

Race: Based on a population pharmacokinetic analysis of pooled data in 765 patients with relapsed or refractory ALL (n=234) and NHL (n=531), race did not significantly affect inotuzumab ozogamicin disposition.

Hepatic insufficiency: No formal pharmacokinetic studies of BESPONSA have been conducted

in patients with hepatic impairment.

Based on a population pharmacokinetic analysis of pooled data in 765 patients with relapsed or refractory ALL (n=234) and NHL (n=531), the clearance of inotuzumab ozogamicin in patients with hepatic impairment defined by National Cancer Institute Organ Dysfunction Working Group (NCI ODWG) category B1 (total bilirubin ≤ ULN and AST > ULN; n=133) or B2 (total bilirubin >1.0-1.5 × ULN and AST any level; n=17) was similar to patients with normal hepatic function (total bilirubin/AST ≤ ULN; n=611) (see **DOSAGE AND ADMINISTRATION, Special Populations and Conditions**, Hepatic insufficiency).

Due to the limited data available in patients with hepatic impairment defined by NCI ODWG category C (total bilirubin >1.5-3 × ULN and AST any level, n=3) and NCI ODWG category D (total bilirubin >3 × ULN and AST any level, n=1), inference on the effect of inotuzumab ozogamicin clearance in these patients cannot be made.

Renal insufficiency: No formal pharmacokinetic studies of BESPONSA have been conducted in patients with renal impairment.

Based on population pharmacokinetic analysis in 765 patients with relapsed or refractory ALL (n=234) and NHL (n=531), the clearance of inotuzumab ozogamicin in patients with mild renal impairment (CrCL 60-89 mL/min; n=237), moderate renal impairment (CrCL 30-59 mL/min; n=122), or severe renal impairment (CrCL 15-29 mL/min; n=4) was similar to patients with normal renal function (CrCL ≥90 mL/min; n=402).

Due to the limited data available in patients with severe renal impairment (CrCL 15-29 mL/min; n=4), inference on the effect of inotuzumab ozogamicin in these patients cannot be made (see **DOSAGE AND ADMINISTRATION, Special Populations and Conditions**, Renal insufficiency). The safety and efficacy of inotuzumab ozogamicin have not been studied in patients with end stage renal disease.

STORAGE AND STABILITY

Store in a refrigerator (2-8˚C).

Do not freeze.

Store in the original carton in order to protect from light.

Table 7 below shows the storage times and conditions for reconstitution, dilution, and administration of BESPONSA.

Table 7. Storage Times and Conditions for Reconstituted and Diluted BESPONSA Solution

BESPONSA must be protected from light during reconstitution, dilution and administration.
Maximum time from reconstitution through administration is 8 hours with up to 4 hours between reconstitution and dilution.

Reconstituted solution	Diluted solution	
	After dilution	**Administration**
Use immediately or after being stored in a refrigerator (2-8°C) for up to 4 hours. **Do not freeze.**	Use diluted solution immediately or after being stored at room temperature (20-25°C) or in a refrigerator (2-8°C). **Do not freeze.**	If the diluted solution is stored in a refrigerator (2-8°C), bring it to room temperature (20-25°C) for approximately 1 hour prior to administration.

SPECIAL HANDLING INSTRUCTIONS

See **DOSAGE AND ADMINISTRATION, Instructions for Reconstitution, Dilution, and Administration**

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each BESPONSA carton contains 1 BESPONSA single-dose vial containing a sterile, preservative-free, white to off-white lyophilized cake or powder. Each vial delivers 0.9 mg inotuzumab ozogamicin. The following non-medicinal ingredients are contained in the vial: sucrose, polysorbate 80, sodium chloride, and tromethamine.

The container is a Type I amber glass vial with chlorobutyl rubber stoppers and crimp seal with flip-off cap.

PART II: SCIENTIFIC INFORMATION

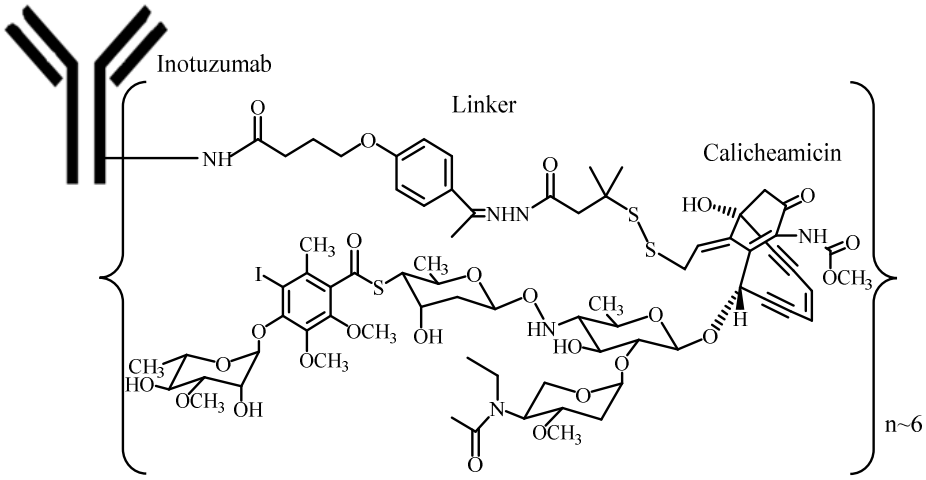
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: inotuzumab ozogamicin

Description and structural formula:

Inotuzumab ozogamicin is a CD22-directed ADC consisting of 3 components: 1) the recombinant humanized IgG4 kappa antibody inotuzumab, specific for human CD22, 2) N-acetyl-gamma-calicheamicin that causes DNA double strand-breaks, and 3) an acid-cleavable linker composed of the condensation product of 4-(4'-acetylphenoxy)-butanoic acid (AcBut) and 3-methyl-3-mercaptobutane hydrazide (known as dimethylhydrazide) that covalently attaches N-acetyl-gamma-calicheamicin to inotuzumab.



Physiochemical properties: Inotuzumab ozogamicin has an approximate molecular weight of 160 kDa. Approximately 6 molecules of calicheamicin derivative are attached to each antibody molecule. Inotuzumab ozogamicin is produced by chemical conjugation of the antibody and small molecule components. The antibody is produced by mammalian (Chinese hamster ovary) cells, and the semisynthetic calicheamicin derivative is produced by microbial fermentation followed by synthetic modification.

CLINICAL TRIALS

Patients with Relapsed or Refractory ALL Who Have Received 1 or 2 Prior Treatment Regimens for ALL – B1931022

Study design and patient demographics

The safety and efficacy of BESPONSA in patients with relapsed or refractory ALL were evaluated in a randomized, open-label, international, multicenter Phase 3 study (B1931022). Patients were stratified at randomization based on duration of first remission (< 12 months or ≥ 12 months, salvage treatment (Salvage 1 or 2) and patient age at randomization (< 55 or ≥ 55 years). Patients (n=326) were ≥18 years of age with Philadelphia chromosome-negative or Philadelphia chromosome-positive relapsed or refractory B-cell precursor ALL. All patients were required to have ≥5% bone marrow blasts and to have received 1 or 2 previous induction chemotherapy regimens for ALL. Patients with Philadelphia chromosome-positive B-cell precursor ALL were required to have disease that failed treatment with at least 1 tyrosine kinase inhibitor and standard chemotherapy. All evaluable patients had B-cell precursor ALL that expressed CD22, with ≥90% of evaluable patients exhibiting ≥70% leukemic blast CD22 positivity prior to treatment, as assessed by flow cytometry performed at a central laboratory. Table 3 shows the dosing regimen used to treat patients.

The co-primary endpoints were CR/CRi, assessed by a blinded independent endpoint adjudication committer (EAC) and OS. The secondary endpoints included minimal residual disease (MRD) negativity, duration of remission (DoR), and the number of patients that proceeded to hematopoietic stem cell transplant. CR/CRi, MRD, and DoR were analyzed in the initial 218 randomized patients and OS was analyzed in all 326 randomized patients.

Among the initial 218 randomized patients who received BESPONSA (N=109) or Investigator's choice of chemotherapy including FLAG, MXN/Ara-C, or HIDAC (N=109), and who were assessed for CR/CRi by the Endpoint Adjudication Committee (EAC), 142 (65%) patients had received 1 prior treatment regimen for ALL and 74 (34%) patients had received 2 prior treatment regimens for ALL. The median age was 47 years (range: 18-79 years), 186 (79%) patients had Philadelphia chromosome-negative ALL, 133 (61%) patients had a duration of first remission <12 months, and 39 (18%) patients had undergone a HSCT prior to receiving BESPONSA or Investigator's choice of chemotherapy.

Among all 326 patients who were randomized to receive BESPONSA (N=164) or Investigator's choice of chemotherapy (N=162), 215 (66%) patients had received 1 prior treatment regimen for ALL and 108 (33%) patients had received 2 prior treatment regimens for ALL. The median age was 47 years (range: 18-79 years), 276 (85%) patients had Philadelphia chromosome-negative ALL, 206 (63%) patients had a duration of first remission <12 months, and 55 (18%) patients had undergone a HSCT prior to receiving BESPONSA or Investigator's choice of chemotherapy.

Overall, the efficacy of BESPONSA was established on the basis of CR/CRi, and CR, the duration of CR/CRi and CR, and proportion of MRD-negative CR/CRi and CR (< 1 x 10^{-4} of bone marrow nucleated cells by flow cytometry) in the first 218 patients randomized.

Study results

Table 8 shows the efficacy results from study B1931022.

Table 8. Efficacy Results in Patients With Relapsed or Refractory B-Cell Precursor ALL Who Received BESPONSA or Investigator's Choice of Chemotherapy (FLAG, MXN/Ara-C, or HIDAC)

	CR[a]		CRi[b]		CR/CRi[a,b]	
	BESPONSA (N=109)	HIDAC, FLAG, or MXN/Ara-C (N=109)	BESPONSA (N=109)	HIDAC, FLAG or MXN/Ara-C (N=109)	BESPONSA (N=109)	HIDAC, FLAG, or MXN/Ara-C (N=109)
Responding (CR/CRi) patients						
n (%) [95% CI]	39 (35.8) [26.8-45.5]	19 (17.4) [10.8-25.9]	49 (45.0) [35.4-54.8]	13 (11.9) [6.5-19.5]	88 (80.7) [72.1-87.7]	32 (29.4) [21.0-38.8]
Rate difference[c] (97.5% CI)[c]					51.4 (38.4-64.3)	
p-value[d]					<0.0001	
MRD-negativity[e]						
n	35	6	34	3	69	9
Rate[f] (%) [95% CI]	35/39 (89.7) [75.8-97.1]	6/19 (31.6) [12.6-56.6]	34/49 (69.4) [54.6-81.7]	3/13 (23.1) [5.0-53.8]	69/88 (78.4) [68.4-86.5]	9/32 (28.1) [13.7-46.7]
DoR[g]						
n	39	18	45	14	84	32
Median, months [95% CI]	8.0 [4.9-10.4]	4.9 [2.9-7.2]	4.6 [3.7-5.7]	2.9 [0.6-5.7]	5.4 [4.2-8.0]	3.5 [2.9-6.6]

Abbreviations: CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete hematologic recovery; DoR=duration of remission; EAC=Endpoint Adjudication Committee; FLAG=fludarabine + cytarabine + granulocyte colony-stimulating factor; HIDAC=high-dose cytarabine; HR=hazard ratio; MRD=minimal residual disease; MXN/AraC=mitoxantrone + cytarabine; N/n=number of patients;

[a] CR, per EAC, was defined as <5% blasts in the bone marrow and the absence of peripheral blood leukemic blasts, full recovery of peripheral blood counts (platelets ≥100 × 10^9/L and absolute neutrophil counts [ANC] ≥1 × 10^9/L) and resolution of any extramedullary disease (Cycle 1 extramedullary disease status).

[b] CRi, per EAC, was defined as <5% blasts in the bone marrow and the absence of peripheral blood leukemic blasts, partial recovery of peripheral blood counts (platelets <100 × 10^9/L and/or ANC <1 × 10^9/L) and resolution of any extramedullary disease (Cycle 1 extramedullary disease status).

[c] The 97.5% confidence interval for the difference in CR/CRi rate was calculated asymptotically based on normal approximation.

[d] 1-sided p-value using Chi-squared test.

[e] MRD-negativity was defined by flow cytometry as leukemic cells comprising <1 × 10^{-4} (<0.01%) of bone marrow nucleated cells.

[f] Rate was defined as the number of patients who achieved MRD negativity divided by the total number of patients who achieved CR/CRi per EAC.

[g] DoR, based on a later cutoff date than the CR/CRi, was defined for patients who achieved CR/CRi per Investigator's assessment as time since first response of CR[a] or CRi[b] per Investigator's assessment to the date of a PFS event or censoring date if no PFS event was documented.

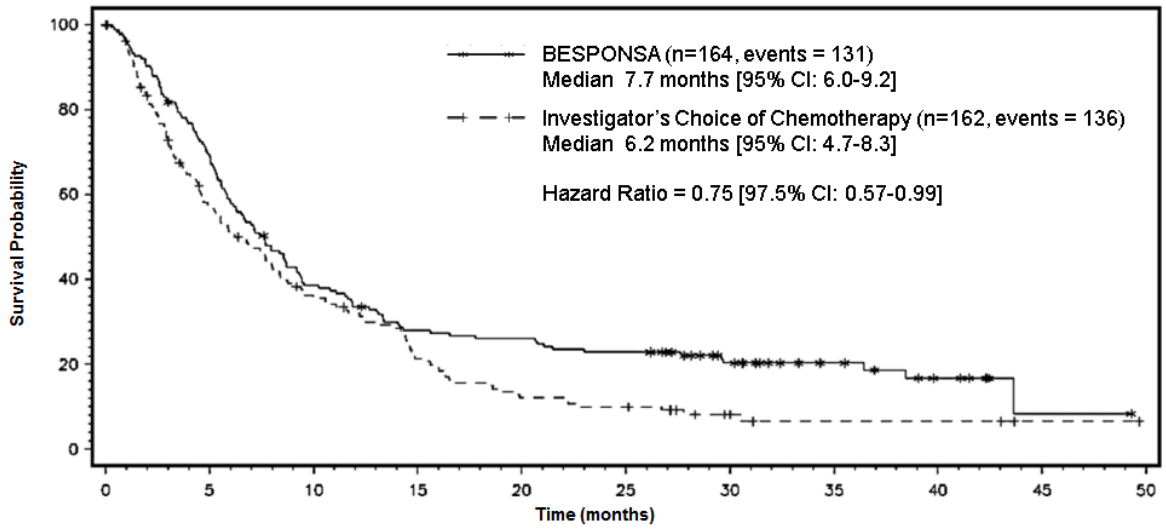
Among the initial 218 randomized patients, 64/88 (73%) and 21/88 (24%) of responding patients per EAC achieved CR/CRi in Cycles 1 and 2, respectively, in the BESPONSA arm, and 29/32 (91%) and 1/32 (3%) of responding patients per EAC achieved a CR/CRi in Cycles 1 and 2, respectively, in the Investigator's choice of chemotherapy arm.

CR/CRi, MRD, and DoR results in the initial 218 randomized patients were consistent with those seen in all 326 randomized patients.

Overall, 79/164 (48.2%) patients in the inotuzumab ozogamicin arm and 35/162 (21.6%) patients in the Investigator's choice of chemotherapy arm had a follow-up HSCT.

Figure 1 shows the analysis of overall survival (OS). The analysis of OS did not meet the pre-specified boundary for statistical significance.

Figure 1. Kaplan-Meier Curve for Overall Survival (Intent-to-Treat Population)



Number of patients at risk

BESPONSA	164	112	62	44	41	36	23	13	7	1	0
Control	162	85	51	30	17	14	5	3	3	1	0

TOXICOLOGY

Repeat-dose toxicity

In repeat-dose toxicity studies in rats and monkeys up to 26 weeks in duration, primary target organs included the liver (liver enzyme elevations, sinusoidal dilation with hepatocyte atrophy, hepatocyte hypertrophy and karyomegaly, and angiectasis), bone marrow and lymphoid organs (hypocellularity), and hematologic changes (reduced platelets, red blood cell [RBC] mass, and lymphocytes). Other toxicity including peripheral and central axonal degeneration and renal nephropathy were observed in rats only, and glomerulonephritis with multisystemic vasculitis was identified in 1 monkey. Other observed changes included male and female reproductive organ effects and preneoplastic and neoplastic lesions (see below). The reversibility of axonal degeneration and liver findings were not established following a 4-week non-dosing period in rats administered 4.07 mg/m^2/week (approximately 21 times the human clinical exposure based on AUC), whereas partial to full reversal of effects on the hematolymphopoietic system and kidney were observed in rats and monkeys and in liver in monkeys.

Genotoxicity

Inotuzumab ozogamicin was clastogenic in vivo in the bone marrow of male mice that received single doses ≥1.14 mg/m^2. This is consistent with the known induction of DNA breaks by calicheamicin. N-acetyl-gamma-calicheamicin dimethylhydrazide (the cytotoxic agent released from inotuzumab ozogamicin) was mutagenic in the Ames assay.

Carcinogenicity

Formal carcinogenicity studies have not been conducted with inotuzumab ozogamicin. In toxicity studies, rats were dosed weekly for 4 or 26 weeks with inotuzumab ozogamicin at doses up to 4.07 mg/m^2/week and 0.727 mg/m^2/week, respectively. After 4 or 26 weeks of dosing, rats developed oval cell hyperplasia, altered cell foci, and hepatocellular adenomas in the liver at ≥0.073 mg/m^2/week (approximately 0.3 times the human clinical exposure based on AUC). In 1 monkey a focus of hepatocellular alteration was detected at 0.732 mg/m^2/week (approximately 3.1 times the human clinical exposure based on AUC) at the end of the 26-week dosing period. The relevance of these animal findings to humans is uncertain.

Reproduction toxicity

Administration of 0.109 mg/m^2/day of inotuzumab ozogamicin (approximately 2.3 times the human clinical exposure based on AUC) prior to mating and during the first week of gestation resulted in embryo-fetal toxicity, including increased resorptions and decreased viable embryos. Fetal growth retardation in rats also occurred at 0.036 mg/m^2/day (approximately 0.4 times the human clinical exposure based on AUC).

Inotuzumab ozogamicin is considered to have the potential to impair reproductive function and fertility in men and women based on nonclinical findings. In repeat dose toxicity studies in rats and monkeys, female reproductive findings included atrophy of ovaries, uterus, vagina, and mammary gland. The no observed adverse effect level (NOAEL) for the effects on female reproductive organs was 0.727 mg/m^2/week in the rat and 0.732 mg/m^2/week in the monkey (approximately 2.2 and 3.1 times the human clinical exposure based on AUC, respectively). In repeat dose toxicity studies in rats, male reproductive findings included testicular degeneration associated with hypospermia, and prostatic and seminal vesicle atrophy were observed at ≥0.073 mg/m^2/week (approximately 0.3 times the human clinical exposure based on AUC); the NOAEL was not identified.

REFERENCES

DiJoseph JF, Dougher MM, Armellino DC, et al. Therapeutic potential of CD22-specific antibody-targeted chemotherapy using inotuzumab ozogamicin (CMC-544) for the treatment of acute lymphoblastic leukemia. Leukemia 2007;21:2240–2245.

De Vries JF, Zwaan CM, De Bie M, et al. The novel calicheamicin-conjugated CD22 antibody inotuzumab ozogamicin (CMC-544) effectively kills primary pediatric acute lymphoblastic leukemia cells. Leukemia 2012;26(2):255-264.

Kantarjian H, Thomas D, Jorgensen J, et al. Results of inotuzumab ozogamicin, a CD22 monoclonal antibody, in refractory and relapsed acute lymphocytic leukemia. Cancer 2013;119:2728-2736.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Pr BESPONSA™
inotuzumab ozogamicin for injection

Read this carefully before you start taking **BESPONSA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **BESPONSA**.

Serious Warnings and Precautions

BESPONSA can cause serious side effects that can be severe, life-threatening, or lead to death, including:

- Post-bone marrow transplant non-relapse death (which means death after bone marrow transplant in the absence of progression of your disease)
- Liver toxicity, including a condition called venoocclusive disease (VOD), in which the blood vessels in the liver become damaged because of blood clots
- Low number of blood cells known as neutrophils, red blood cells, white blood cells, lymphocytes, or a low number of blood cells known as platelets (with signs and symptoms such as infection, fever, bruising easily or bleeding)
- Tumor lysis syndrome (complications occurring after cancer treatment leading to increased blood levels of potassium, uric acid, and phosphorus and decreased blood levels of calcium)
- Infusion-related reactions (with signs and symptoms such as fever and chills during or shortly after the BESPONSA infusion)
- QT interval prolongation (with signs and symptoms such as dizziness, light headedness, and loss of consciousness)

What is BESPONSA used for?

The active substance 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 a certain type of leukemia called acute lymphoblastic leukemia (ALL). ALL is a cancer of the blood where you have too many white blood cells. BESPONSA is intended for the treatment of ALL in adult patients whose ALL has come back after a previous treatment (relapse) or if the ALL has not responded to the first treatment (refractory).

How does BESPONSA work?

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

What are the ingredients in BESPONSA?

Medicinal ingredients: Inotuzumab ozogamicin.

Non-medicinal ingredients: Polysorbate 80, sodium chloride, sucrose and tromethamine.

BESPONSA comes in the following dosage forms:
BESPONSA is supplied as a white to off-white lyophilized cake or powder in a glass vial for solution for infusion. There is 1 amber glass vial with chlorobutyl rubber stopper and flip-off cap. Each vial delivers 0.9 mg inotuzumab ozogamicin.

Do not use BESPONSA if:

- you are allergic to inotuzumab ozogamicin or any of the other ingredients of this medicine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take BESPONSA. Talk about any health conditions or problems you may have, including 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 (VOD), a condition in which the blood vessels in the liver become damaged and obstructed by blood clots. VOD 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. 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 cells 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 during or shortly after the BESPONSA infusion.
- have signs and symptoms of a syndrome known as tumor lysis syndrome, which may be associated with a variety of symptoms in the stomach and intestines (for example, nausea, vomiting, diarrhea), 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.

Other warnings you should know about:

Pregnancy, breastfeeding and fertility

- If you are pregnant or breastfeeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before you are given this medicine.
- You must avoid becoming pregnant or fathering a child. Women must use effective contraception during treatment and at least 8 months after the last dose of treatment. Men must use effective contraception during treatment and at least 5 months after the last dose of treatment. Contact your doctor immediately if you or your partner becomes pregnant while taking this medicine.
- Seek advice regarding fertility preservation before treatment.
- If you need treatment with BESPONSA, you must stop breastfeeding 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**), take special care when driving or using machines.

Vaccinations

- You should not receive a live vaccine within 2 weeks prior to the start of BESPONSA treatment, during treatment, and until recovery of cells called B-lymphocytes following your last dose of BESPONSA.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with BESPONSA:

- It is not known which medications interact with BESPONSA.
- Medicinal products known to prolong QT interval or to induce Torsade de Pointes.

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 are going to receive a stem cell transplant, you may receive 2 cycles or a maximum of 3 cycles of treatment.
- If the medicine works well but are not going to receive a stem cell transplant, 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.

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).

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

Usual dose:
Your doctor will decide on the correct dose.

Overdose:

If you think you have received too much BESPONSA, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Speak with your healthcare professional as soon as possible if you miss a dose of BESPONSA.

What are possible side effects from using BESPONSA?
Like all medicines, this medicine can cause side effects, although not everybody experiences them. Some of these side effects may be serious.

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

- venoocclusive liver disease
- 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.
- infusion-related reaction
- tumor lysis syndrome.
- QT interval prolongation

Other side effects may include:

Very common side effects (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 cell) which may result in a tendency to develop infections
- decreased appetite
- reduced number of red blood cells which may result in fatigue and shortness of breath
- headache
- bleeding
- pain in the abdomen
- vomiting
- diarrhea
- nausea
- mouth inflammation
- constipation
- raised bilirubin level leading to a yellowish color 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

Less 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/stomach
- 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

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Veno-occlusive liver disease, a serious condition that 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; this condition may occur during			√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
treatment with BESPONSA or after subsequent treatment with a stem cell transplant			
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		√	
LESS COMMON			
Signs and symptoms of an infusion-related reaction such as fever and chills during or shortly after the BESPONSA infusion		√	
Signs and symptoms of tumor lysis syndrome, which may be associated with symptoms in the stomach and intestines (for example, nausea, vomiting, diarrhea), 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			√
Signs and symptoms of QTc prolongation (for example dizziness, light headedness, and fainting)		√	
Signs and symptoms of PR interval prolongation (typically asymptomatic, but could progress to include for example dizziness, light headedness, and		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
fainting)			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect™;
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Patient Side Effect Reporting Form are available at MedEffect™ .

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Unopened Vial

Store in a refrigerator (2-8°C). Do not freeze.

Store in the original carton in order to protect from light.

BESPONSA will be prepared in an infusion container by a pharmacist and then delivered to the healthcare professional who will administer the medication to you as an intravenous infusion at the hospital.

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.

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.

Keep out of reach and sight of children.

If you want more information about BESPONSA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.pfizer.ca, or by calling 1-800-463-6001.

This leaflet was prepared by Pfizer Canada Inc.

Last Revised: March 15, 2018.