▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – BESPONSA® (INOTUZUMAB OZOGAMICIN (rch))

WARNING:

- **Hepatotoxicity, including fatal and life-threatening hepatic venoocclusive disease has occurred in patients treated with BESPONSA.**
- **An increased risk of post-haematopoietic stem cell transplant (HSCT) non-relapse mortality has been observed in patients treated with BESPONSA.**

1. NAME OF THE MEDICINE

Inotuzumab ozogamicin (rch)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BESPONSA (inotuzumab ozogamicin) is a CD22-directed antibody-drug conjugate (ADC) consisting of 3 components:

1) a recombinant humanised immunoglobulin class G subtype 4 (IgG4) kappa antibody inotuzumab, produced in Chinese hamster ovary cells by recombinant deoxyribonucleic acid (DNA) technology, specific for human CD22,

2) a semisynthetic calicheamicin derivative, N-acetyl-gamma-calicheamicin, produced by microbial fermentation followed by synthetic modification, that causes double-stranded DNA 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.

Each vial contains 1 mg inotuzumab ozogamicin.

After reconstitution with 4 mL of sterile water for injection, 1 mL of solution contains 0.25 mg inotuzumab ozogamicin. The drug product pH is approximately 8.0.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Powder for injection.

BESPONSA is supplied for intravenous infusion as 1 mg (protein equivalent) of white to off-white lyophilised cake or powder in a single dose vial for reconstitution and dilution.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

BESPONSA is indicated for the treatment of adults with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukaemia (ALL).

4.2 Dose and method of administration

Use of BESPONSA should be initiated and supervised by a physician experienced in the treatment of haematological malignancies.

Premedication

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 Section 4.4 Special warnings and precautions for use, Infusion Related Reactions). Patients should be observed during and for at least 1 hour after the end of infusion for symptoms of infusion related reactions (see Section 4.4 Special warnings and precautions for use, Infusion Related Reactions).

Recommended Dosage Regimen

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

For patients proceeding to HSCT, the recommended duration of treatment with BESPONSA is 2 cycles. A third cycle may be considered for those patients who do not achieve a CR or CRi and MRD negativity after 2 cycles (see Section 4.4 Special warnings and precautions for use, Hepatotoxicity, including VOD/SOS).

For patients 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 1 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 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 1. 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[d] or CRi[e]:			
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 haematologic 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, and/or to allow for recovery from toxicity, the cycle length may be extended up to 28 days (i.e., 7-day treatment-free interval starting on Day 21).

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

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

Dosage adjustments

Dose modification of BESPONSA may be required based on individual safety and tolerability (see Section 4.4 Special warnings and precautions for use). Management of some adverse drug reactions may require dosing interruptions and/or dose reductions, or permanent discontinuation of BESPONSA (see Section 4.4 Special warnings and precautions for use and Section 4.8 Adverse effects (undesirable effects)). If the dose is reduced due to BESPONSA-related toxicity, the dose must not be re-escalated.

Table 2 and Table 3 show the dose modification guidelines for haematologic and nonhaematologic 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 nonhaematologic toxicities.

Table 2. Dose Modifications for Haematologic Toxicities

Haematologic Toxicity	Dose Modification(s)
If prior to BESPONSA treatment:	
ANC was $\geq 1 \times 10^9$/L	If ANC decreases, interrupt the next cycle of treatment until recovery of ANC to $\geq 1 \times 10^9$/L.
Platelet count was $\geq 50 \times 10^9$/L[a]	If platelet count decreases, interrupt the next cycle of treatment until platelet count recovers to $\geq 50 \times 10^9$/L[a].
ANC was $< 1 \times 10^9$/L and/or platelet count was $< 50 \times 10^9$/L[a]	If ANC and/or platelet count decreases, 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 $\geq 1 \times 10^9$/L and platelet count recovers to $\geq 50 \times 10^9$/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 3. Dose Modifications for Nonhaematologic Toxicities

Nonhaematologic Toxicity	Dose Modification(s)
VOD/SOS or other severe liver toxicity	Permanently discontinue treatment (see Section 4.4 Special warnings and precautions for use, Hepatotoxicity, including VOD/SOS).
Total bilirubin >1.5 × ULN and AST/ALT >2.5 × ULN	Interrupt dosing until recovery of total bilirubin to ≤1.5 × ULN and AST/ALT to ≤2.5 × ULN prior to each dose unless due to Gilbert's syndrome or haemolysis. Permanently discontinue treatment if total bilirubin does not recover to ≤1.5 × ULN or AST/ALT does not recover to ≤2.5 × ULN (see Section 4.4 Special warnings and precautions for use, 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 Section 4.4 Special warnings and precautions for use, Infusion Related Reactions).
Grade ≥2[a] nonhaematologic toxicity (BESPONSA-related)	Interrupt treatment until recovery to Grade 1 or pre-treatment grade levels prior to each dose.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal; VOD/SOS=venoocclusive liver disease/sinusoidal obstruction syndrome.

[a] Severity grade according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0.

Table 4 shows the dose modification guidelines depending on the duration of dosing interruptions due to toxicity.

Table 4. Dose Modifications Depending on Duration of Dosing Interruption Due to Toxicity

Duration of Dose Interruption Due to Toxicity	**Dose Modification(s)**
<7 days (within a cycle)	Interrupt the next dose (maintain a minimum of 6 days between doses).
≥7 days	Omit the 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.

Children and Adolescents

The safety and efficacy of BESPONSA in children and adolescents (<18 years) have not been established.

Use in Hepatic Impairment

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 Section 5.2 Pharmacokinetic properties, Special Populations, Hepatic Impairment).

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 haemolysis (see Table 1). 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 1 and Section 4.4 Special warnings and precautions for use, Hepatotoxicity, including VOD/SOS).

Use in Renal Impairment

No adjustment to the starting dose is required when administering BESPONSA to patients with mild, moderate, or severe renal impairment (CLcr 60-89 mL/min, 30-59 mL/min, or 15-29 mL/min, respectively) (see Section 5.2 Pharmacokinetic properties, Special Populations, Renal Impairment). The safety and efficacy of BESPONSA have not been studied in patients with end-stage renal disease.

Use in the Elderly

No adjustment to the starting dose is required based on age (see Section 5.2 Pharmacokinetic properties, Special Populations, Age, Race and Gender).

Increased age may be associated with an increased risk of VOD/SOS after HSCT (see Section 4.4 Special warnings and precautions for use, Hepatotoxicity, including VOD/SOS).

Instructions for Reconstitution, Dilution and Administration

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

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 1 mg vial with 4 mL of Sterile Water for Injection to obtain a solution of 0.25 mg/mL of BESPONSA.
- Gently swirl the vial to aid dissolution. **DO NOT SHAKE**.
- Inspect the reconstituted solution for particulates and discolouration. The reconstituted solution should be clear to slightly cloudy, colourless, 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 BESPONSA solution left in the vial.
- Add the reconstituted solution to an infusion container with 0.9% Sodium Chloride for Injection to a total nominal volume of 50 mL. The final concentration should be between 0.01 and 0.1 mg/mL. **PROTECT FROM LIGHT**. An infusion container made of polyvinyl chloride (PVC) (di(2-ethylhexyl) phthalate [DEHP]- or non-DEHP-containing), polyolefin (polypropylene and/or polyethylene), or ethylene vinyl acetate (EVA) is recommended.
- Gently invert the infusion container to mix the diluted solution. **DO NOT SHAKE**.

- The diluted solution 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.

- 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 aluminium foil) during infusion. The infusion line does not need to be protected from light.

- Infuse the diluted solution for 1 hour at a rate of 50 mL/h at room temperature (20-25°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.

BESPONSA contains no antimicrobial preservative and is for use in one patient on one occasion only.

Table 9 in Section 6.4 Special precautions for storage contains a summary of storage times and conditions for reconstitution, dilution, and administration of BESPONSA.

4.3 Contraindications

- Hypersensitivity to inotuzumab ozogamicin or to any of the excipients
- Patients who have experienced prior confirmed severe or ongoing venoocclusive liver disease/sinusoidal obstruction syndrome (VOD/SOS)
- Patients with serious ongoing hepatic disease (e.g., cirrhosis, nodular regenerative hyperplasia, active hepatitis).

4.4 Special warnings and precautions for use

Hepatotoxicity, including Venoocclusive Liver Disease (VOD)/Sinusoidal Obstruction Syndrome (SOS)

In a randomised clinical study of BESPONSA in patients with relapsed or refractory ALL (B1931022), hepatotoxicity, including severe, life threatening, and sometimes fatal hepatic

VOD/SOS was observed in 23/164 patients (14%) in the BESPONSA arm during or following treatment or following a HSCT after completion of treatment. VOD was reported up to 56 days after the last dose during treatment or during follow-up without an intervening HSCT. The median time from subsequent HSCT to onset of VOD was 15 days (range: 3-57 days). In the BESPONSA arm, among the 79 patients who proceeded to a subsequent HSCT, VOD was reported in 18/79 patients (23%), and among all 164 patients treated, VOD was reported in 5/164 patients (3%) during study therapy or in follow-up without an intervening HSCT (see Section 4.8 Adverse effects (undesirable effects)).

In Study B1931022, increases in liver tests, were reported. Grade 3/4 AST, ALT, and total bilirubin abnormal liver tests occurred in 7/160 (4%), 7/161 (4%), and 8/161 patients (5%), respectively (see Section 4.8 Adverse effects (undesirable effects)).

Some 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.

Prior HSCT may be associated with an increased risk of VOD/SOS (see Section 4.8 Adverse effects (undesirable effects)).

Among patients who proceed to HSCT, use of HSCT conditioning regimens containing 2 alkylating agents and last total bilirubin level ≥ 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), 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 Section 4.2 Dose and method of administration, Dosage adjustments).

Patients who have experienced prior confirmed severe or ongoing VOD/SOS or patients with serious ongoing liver disease (e.g., cirrhosis, nodular regenerative hyperplasia, active hepatitis) should not be treated with BESPONSA (see Section 4.3 Contraindications).

Carefully consider the benefit/risk before administering BESPONSA to patients who have experienced mild/moderate VOD/SOS or patients with less serious ongoing hepatic disease.

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 Section 4.2 Dose and method of administration, Dosage adjustments).

Particular attention should be paid when administering BESPONSA to patients who are older, have had a prior HSCT, are in later lines of salvage, or have a prior history of liver disease and/or hepatitis. Due to the risk of VOD/SOS, for patients proceeding to HSCT, the 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 Section 4.2 Dose and method of administration, Recommended Dosage Regimen). Avoid the use of HSCT conditioning regimens containing 2 alkylating agents.

Permanently discontinue treatment if VOD/SOS occurs (see Section 4.2 Dose and method of administration, Dosage adjustments). If severe VOD/SOS occurs, treat according to standard medical practice.

Increased Risk of Post-Transplant Non-Relapse Mortality

In 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.

Monitor closely for toxicities post-HSCT, including signs and symptoms of infection and VOD/SOS (see Section 4.8 Adverse effects (undesirable effects)).

Myelosuppression/Cytopenias

In study B1931022, neutropenia, thrombocytopenia, anaemia, leukopenia, febrile neutropenia, lymphopenia, and pancytopenia, some of which were life-threatening, were reported (see Section 4.8 Adverse effects (undesirable effects)).

Complications associated with neutropenia and thrombocytopenia (including infections and bleeding/haemorrhagic events, respectively) were reported in some patients (see Section 4.8 Adverse effects (undesirable effects)). Infections, including serious infections, some of which were life-threatening or fatal, were reported. Fatal infections included pneumonia, neutropenic sepsis, sepsis, septic shock, and pseudomonal sepsis. Bacterial, viral, and fungal infections were also reported.

Monitor complete blood counts prior to each dose of BESPONSA and monitor for signs and symptoms of infection, bleeding/haemorrhage, 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/haemorrhage, or other effects of myelosuppression, including severe neutropenia or thrombocytopenia, may require dosing interruption, dose reduction, or permanent discontinuation of BESPONSA (see Section 4.2 Dose and method of administration, Dosage adjustments).

Infusion Related Reactions

In study B1931022, infusion related reactions were reported (see Section 4.8 Adverse effects (undesirable effects)). 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 (see Section 4.2 Dose and method of administration, Premedication).

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 hypotension, hot flush, 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 or administration of steroids and antihistamines. For severe or life-threatening infusion reactions, permanently discontinue BESPONSA (see Section 4.2 Dose and method of administration, Dosage adjustments).

Tumour Lysis Syndrome

In study B1931022, tumour lysis syndrome (TLS), which may be life-threatening or fatal, was reported (see Section 4.8 Adverse effects (undesirable effects)). 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.

QT Interval Prolongation

In study B1931022, increases in QTcF interval of ≥60 msec from baseline were measured in some patients. No patient had QTcF values >500 msec (see Section 5.1 Pharmacodynamic properties, Cardiac Electrophysiology). Grade 2 QT prolongation was reported. No Grade ≥3 QT prolongation or event of Torsade de Pointes were reported (see Section 4.8 Adverse effects (undesirable effects)).

BESPONSA should be administered with caution in patients who have a history of, or predisposition for QT interval prolongation, who are taking medicinal products that are known to prolong QT interval, and in patients with electrolyte disturbances (see Section 4.5 Interactions with other medicines and other forms of interactions. Electrocardiograms (ECGs) and electrolytes should be obtained prior to the start of treatment and periodically monitored during treatment (see Section 5.1 Pharmacodynamic properties, Cardiac Electrophysiology).

Increased Amylase and Lipase

In study B1931022, increases in amylase and lipase were reported in 8 (5%) and 15 (9%) patients receiving BESPONSA, respectively (see Section 4.8 Adverse effects (undesirable effects)). Patients should be monitored for increases in amylase and lipase. Potential hepatobiliary disease should be evaluated and treated according to standard medical practice.

Paediatric Use

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

Use in the Elderly

Based on a population pharmacokinetic analysis in 765 patients, no adjustment to the starting dose is required based on age (see Section 5.2 Pharmacokinetic properties, Special Populations, Age, Race and Gender).

In a randomised clinical study of BESPONSA for the treatment of patients with ALL (B1931022), 30/164 (18%) patients treated with BESPONSA were ≥65 years of age. Although no overall differences were observed in the safety and efficacy (CR/CRi and OS) of BESPONSA between patients who were <65 and ≥65 years of age, increased age may be associated with an increased risk of VOD/SOS after HSCT (see Section 4.4 Special warnings and precautions for use, Hepatotoxicity, including VOD/SOS).

Use in Hepatic Impairment

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 Section 5.2 Pharmacokinetic properties, Special Populations, Hepatic Impairment).

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. Management of such patients may require dosing interruption or permanent discontinuation of BESPONSA (see Section 4.2 Dose and method of administration, Dosage adjustments and Section 4.4 Special warnings and precautions for use, Hepatotoxicity, including VOD/SOS).

Use in Renal Impairment

No adjustment to the starting dose is required when administering BESPONSA to patients with mild, moderate, or severe renal impairment (CLcr 60-89 mL/min, 30-59 mL/min, or 15-29 mL/min, respectively) (see Section 5.2 Pharmacokinetic properties, Special Populations, Renal Impairment). The safety and efficacy of BESPONSA have not been studied in patients with end-stage renal disease.

Effects on Laboratory Tests

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

4.5 Interactions with other medicines and other forms of interactions

No clinical drug interaction studies have been performed with BESPONSA.

In a randomised clinical study of BESPONSA in patients with relapsed or refractory ALL (B1931022), prolonged QT interval was observed with BESPONSA (see Section 5.1 Pharmacodynamic properties, Cardiac Electrophysiology). Therefore, the concomitant use of

BESPONSA with medicinal products known to prolong QT interval or able to induce Torsades de Pointes should be carefully considered. Monitor the QT interval in case of combinations of such medicinal products (see Section 4.4 Special warnings and precautions for use, QT Interval Prolongation).

Effect of Other Medicines on Inotuzumab Ozogamicin

In vitro, N-acetyl-gamma-calicheamicin dimethylhydrazide is primarily metabolised via nonenzymatic reduction. Therefore, coadministration of BESPONSA with inhibitors or inducers of cytochrome P450 (CYP) or uridine diphosphate glucuronosyltransferase (UGT) drug-metabolising enzymes are unlikely to alter exposure to N-acetyl-gamma-calicheamicin dimethylhydrazide.

Based on a population pharmacokinetic analysis in 736 patients, 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 Inotuzumab Ozogamicin on Other Medicines

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.

Effect 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.

4.6 Fertility, pregnancy and lactation

Effects on fertility

In a female fertility and early embryonic development study, female rats received daily intravenous doses of inotuzumab ozogamicin up to 0.11 mg/m^2 for 2 weeks before mating through Day 7 of pregnancy. An increase in the proportion of resorptions and decrease in the number of viable embryos were observed at the 0.11 mg/m^2 dose level (approximately 3 times the exposure in patients at the maximum recommended dose, based on AUC).

Additional findings in female reproductive organs occurred in repeat-dose toxicology studies and included decreased ovarian and uterine weights, and ovarian and uterine atrophy. Findings in male reproductive organs occurred in repeat-dose toxicology studies and included decreased testicular weights, testicular degeneration, hypospermia, and prostatic and seminal vesicle atrophy. Testicular degeneration and hypospermia were non-reversible following a 4-week non-dosing period. In the chronic studies of 26-weeks duration, adverse effects on reproductive organs occurred at ≥0.07 mg/m^2 in male rats (approximately 0.1 times the exposure in patients at the maximum recommended dose, based on AUC).

Based on these findings, female and male fertility may be compromised by treatment with BESPONSA. Both men and women should seek advice for fertility preservation before treatment.

Use in pregnancy – Pregnancy Category D

There are no data in pregnant women using BESPONSA.

In a fertility and early embryonic development study in female rats, inotuzumab ozogamicin was administered intravenously daily for 2 weeks before mating through Day 7 of pregnancy, which resulted in embryo-fetal mortality in the presence of slight maternal toxicity at doses of 0.109 mg/m^2/day with maternal systemic exposures (approximately 3 times the human clinical exposure based on AUC).

In embryo-fetal development studies in rats and rabbits, pregnant animals received daily intravenous doses up to 0.109 mg/m^2/day or 0.145 mg/m^2/day, respectively, during the period of organogenesis. The maternally toxic dose of 0.109 mg/m^2/day was fetotoxic in rats, resulting in fetal growth retardation as evidenced by decreased fetal weights and delayed skeletal ossification. Slight fetal growth retardation in rats also occurred at 0.036 mg/m^2/day (approximately 0.45 times the human clinical exposure based on AUC). At a dose of 0.145 mg/m^2/day in rabbits (approximately 4 times the human clinical exposure based on AUC), there were no effects on embryo-fetal development.

Based on these findings and the genotoxic potential of inotuzumab ozogamicin (see Section 5.3 Preclinical safety data, Genotoxicity), BESPONSA can cause embryo-fetal harm when administered to a pregnant woman.

BESPONSA should not be used during pregnancy unless the potential benefit to the mother outweighs the potential risks to the fetus.

Women of childbearing potential should be advised to use effective contraception to avoid becoming pregnant during treatment with BESPONSA and for at least 8 months after the last dose.

Men with female partners of childbearing potential should be advised to use effective contraception during treatment with BESPONSA and for at least 5 months after the last dose.

Pregnant women, or patients becoming pregnant while receiving BESPONSA, or treated male patients as partners of pregnant women, must be apprised of the potential risk to the fetus.

Use in lactation

There are no data on the presence of inotuzumab ozogamicin 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.

4.7 Effects on ability to drive and use machines

No formal studies have been conducted on effects on the ability to drive and use machines. Patients should be advised that they may experience fatigue during treatment with BESPONSA (see Section 4.8 Adverse effects (undesirable effects)). Therefore, caution is recommended when driving or operating machines.

4.8 Adverse effects (undesirable effects)

The adverse effects described in this section reflect exposure to BESPONSA in 164 patients with relapsed or refractory ALL who participated in a randomised clinical study of BESPONSA versus Investigator's choice of chemotherapy (FLAG, MXN/Ara-C, or HIDAC) (B1931022) (see Section 5.1 Pharmacodynamic properties, Clinical trials).

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 (≥20%) adverse reactions were thrombocytopenia, neutropenia, infection, anaemia, leukopenia, fatigue, haemorrhage, pyrexia, nausea, headache, febrile neutropenia, transaminases increased, abdominal pain, gamma-glutamyltransferase increased, and hyperbilirubinaemia.

In patients who received BESPONSA, the most common (≥2%) serious adverse reactions were infection (23%), febrile neutropenia (11%, haemorrhage (5%), abdominal pain (3%), pyrexia (2%), VOD/SOS (2%), and fatigue (2%).

In patients who received BESPONSA, the most common (≥ 2%) adverse reactions reported as the reason for permanent discontinuation were infection (6%), thrombocytopenia (2%), hyperbilirubinaemia (2%), transaminases increased (2%), and haemorrhage (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%); the most common (≥ 1%) adverse reactions reported as the reason for dose reduction were neutropenia (1%), thrombocytopenia (1%), and transaminases increased (1%).

Tabular Listing of Adverse Reactions

Table 5 shows the adverse reactions with ≥10% incidence reported in patients with relapsed or refractory ALL who received BESPONSA or Investigator's choice of chemotherapy (only adverse reactions with ≥10% incidence in the BESPONSA arm are included).

Table 5. Adverse Reactions With ≥10% 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[b] (N=143)	
	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
Anaemia[f]	36	24	59	47
Leukopenia[g]	35	33	43	42
Febrile neutropenia	26	26	53	53
Lymphopenia[h]	18	16	27	26
Metabolism and nutrition disorders				
Decreased appetite	12	1	13	2
Nervous system disorders				
Headache[i]	28	2	27	1
Vascular disorders				
Haemorrhage[j]	33	5	28	5
Gastrointestinal disorders				
Nausea	31	2	46	0
Abdominal pain[k]	23	3	23	1
Diarrhoea	17	1	38	1
Constipation	16	0	24	0
Vomiting	15	1	24	0
Stomatitis[l]	13	2	26	3
Hepatobiliary disorders				
Hyperbilirubinaemia	21	5	17	6
General disorders and administration site conditions				
Fatigue[m]	35	5	25	3
Pyrexia	32	3	42	6
Chills	11	0	11	0
Investigations				
Transaminases increased[n]	26	7	13	5
Gamma-glutamyltransferase increased	21	10	8	4
Alkaline phosphatase increased	13	2	7	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 inotuzumab ozogamicin, 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.
Severity grade of adverse reactions according to NCI CTCAE version 3.0.
Abbreviations: ALL=acute lymphoblastic leukaemia; FLAG=fludarabine + cytarabine + granulocyte colony-stimulating factor; HIDAC=high dose cytarabine; HSCT=haematopoietic stem cell transplant; MXN/Ara-C=mitoxantrone + cytarabine; N=number of patients; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.
[a] Only adverse reactions with ≥10% incidence in the inotuzumab ozogamicin arm are included.

[b] 19 patients randomised to FLAG, MXN/Ara-C, or HIDAC did not receive treatment.
[c] Infection includes any reported preferred terms for inotuzumab ozogamicin 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] Anaemia includes the following reported preferred terms: Anaemia and Haemoglobin 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] Headache includes the following reported preferred terms: Headache, Migraine, and Sinus headache.
[j] Haemorrhage includes reported preferred terms for inotuzumab ozogamicin retrieved in the Standard MedDRA Query (narrow) for Haemorrhage terms (excluding laboratory terms), resulting in the following preferred terms: Conjunctival haemorrhage, Contusion, Ecchymosis, Epistaxis, Eyelid bleeding, Gastrointestinal haemorrhage, Gastritis haemorrhagic, Gingival bleeding, Haematemesis, Haematochezia, Haematotympanum, Haematuria, Haemorrhage intracranial, Haemorrhage subcutaneous, Haemorrhoidal haemorrhage, Intra-abdominal haemorrhage, Lip haemorrhage, Lower gastrointestinal haemorrhage, Mesenteric haemorrhage, Metrorrhagia, Mouth haemorrhage, Muscle haemorrhage, Oral mucosa haematoma, Petechiae, Post procedural haematoma, Rectal haemorrhage, Shock haemorrhagic, Subcutaneous haematoma, Subdural haematoma, Upper gastrointestinal haemorrhage, and Vaginal haemorrhage.
[k] Abdominal pain includes the following reported preferred terms: Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Oesophageal pain, and Hepatic pain.
[l] Stomatitis includes the following reported preferred terms: Aphthous ulcer, Mucosal inflammation, Mouth ulceration, Oral pain, Oropharyngeal pain, and Stomatitis.
[m] Fatigue includes the following reported preferred terms: Asthenia and Fatigue.
[n] Transaminases increased includes the following reported preferred terms: Aspartate aminotransferase increased, Alanine aminotransferase increased, Hepatocellular injury, and Hypertransaminasaemia.

Listing of Additional Adverse Reactions

Additional adverse reactions (all grades) that were reported in <10% of patients treated with BESPONSA included:

Blood and lymphatic system disorders:

- Common: Pancytopenia (2%; includes the following preferred terms: bone marrow failure, febrile bone marrow aplasia, and pancytopenia).

Metabolism and nutrition disorders:

- Common: Hyperuricaemia (4%), tumour lysis syndrome (2%; see text below and Section 4.4 Special warnings and precautions for use, Tumour Lysis Syndrome).

Gastrointestinal disorders:

- Common: Abdominal distension (6%), ascites (4%).

Hepatobiliary disorders:

- Common: VOD/SOS (3%), includes 1 patient with VOD/SOS that occurred at Day 56 (i.e., not within 42 days of Cycle 1 Day 1) with no intervening HSCT but does not include 18 patients with VOD/SOS that occurred after HSCT (see text below and Section 4.4 Special warnings and precautions for use, Hepatotoxicity, including VOD/SOS).

Investigations:

- Common: Lipase increased (9%), amylase increased (5%), electrocardiogram QT prolonged (1%; see text below and Section 4.4 Special warnings and precautions for use, QT Interval Prolongation).

Injury, poisoning, and procedural complications:

- Common: Infusion related reaction (2%; includes the following preferred terms: hypersensitivity and infusion related reaction) (see text below and Section 4.4 Special warnings and precautions for use, Infusion Related Reactions).

Description of Selected Adverse Reactions

Hepatotoxicity, including Venoocclusive Liver Disease/Sinusoidal Obstruction Syndrome (VOD/SOS)

In study B1931022, VOD/SOS was reported in 23/164 (14%) patients during or following treatment or following a HSCT after completion of treatment. Grade 3/4 AST, ALT, and total bilirubin abnormal liver tests occurred in 7/160 (4%), 7/161 (4%), and 8/161 (5%) patients, respectively.

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.

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).

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 13/68 (19%) patients who only received a HSCT after BESPONSA treatment.

For clinical management of hepatotoxicity, including VOD/SOS, see Section 4.4 Special warnings and precautions for use.

Increased Risk of Post-Transplant Non-Relapse Mortality

In study B1931022, 79/164 patients (48%) in the BESPONSA arm and 35/162 patients (22%) in the Investigator's choice of chemotherapy arm had a follow-up HSCT. Although the overall post-HSCT mortality rate was similar in the BESPONSA arm and Investigator's choice of chemotherapy arm (51/79 [65%] and 23/35 [66%], respectively), the post-HSCT non-relapse mortality rate was higher in the BESPONSA arm compared to the Investigator's choice of chemotherapy arm (31/79 [39%] and 8/35 [23%], respectively).

In the BESPONSA arm, the most common causes of post-HSCT non-relapse mortality included VOD and infections. Five of the 18 VOD events that occurred post-HSCT were fatal. In the BESPONSA arm, among patients with ongoing VOD at time of death, 6 patients 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).

For clinical management of the increased risk of post-transplant non-relapse mortality, see Section 4.4 Special warnings and precautions for use.

Myelosuppression/Cytopenias

In study B1931022, 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.

For clinical management of myelosuppression/cytopenias, see Section 4.4 Special warnings and precautions for use.

Complications associated with neutropenia and thrombocytopenia

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

For clinical management of myelosuppression/cytopenias and associated complications, see Section 4.4 Special warnings and precautions for use.

Infusion Related Reactions

In study B1931022, infusion related reactions, all of which were Grade ≤2 in severity, were reported in 4/164 (2%) patients. These infusion related reactions generally occurred shortly after the end of the BESPONSA infusion and resolved.

For clinical management of infusion related reactions, see Section 4.4 Special warnings and precautions for use.

Tumour Lysis Syndrome

In study B1931022, tumour lysis syndrome (TLS), which may be life-threatening or fatal, was reported in 4/164 (2%) patients. 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.

For clinical management of TLS, see Section 4.4 Special warnings and precautions for use.

QT Interval Prolongation

In study B1931022, increases in QTcF interval of ≥60 msec from baseline were measured in 4/162 (3%) patients. No patient had QTcF values >500 msec. Grade 2 QT prolongation was reported in 2/164 (1%) patients. No Grade ≥3 QT prolongation or event of Torsade de Pointes were reported.

For periodic monitoring of ECG and electrolyte levels, see Section 4.4 Special warnings and precautions for use.

Laboratory Abnormalities

Table 6 shows the clinically important laboratory abnormalities reported in patients with relapsed or refractory ALL who received BESPONSA or Investigator's choice of chemotherapy.

Table 6. 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)

		BESPONSA			FLAG, MXN/Ara-C, or HIDAC	
		All Grades	Grade 3/4		All Grades	Grade 3/4
Laboratory Abnormality[a]	N	%	%	N	%	%
Haematology						
Platelet count decreased	161	98	76	142	100	99
Haemoglobin 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

Severity grade of laboratory abnormalities according to NCI CTCAE version 3.0.
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; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.
[a] Laboratory abnormalities were summarized up to the end of treatment + 42 days but prior to the start of a new anti-cancer therapy.

Immunogenicity

In clinical studies of BESPONSA in patients with relapsed or refractory ALL, 7/236 (3%) patients tested positive for anti-inotuzumab ozogamicin antibodies. No patient tested positive for neutralising 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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 Overdose

Overdoses may result in adverse reactions that are consistent with the reactions observed at the recommended therapeutic dose (see Section 4.8 Adverse effects (undesirable effects)). In the event of an overdose, the infusion should be temporarily interrupted and patients should be monitored for liver and haematological toxicities (see Section 4.2 Dose and method of administration). Reinitiation of BESPONSA at the correct therapeutic dose should be considered when all toxicities have resolved.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action

Inotuzumab ozogamicin is a CD22-targeted antibody-drug conjugate (ADC). Inotuzumab is a humanised IgG4 antibody which specifically recognises human CD22. The small molecule, N-acetyl-gamma-calicheamicin, is a cytotoxic agent that is covalently attached to the antibody via an acid-cleavable linker. Nonclinical data suggest that the anticancer activity of inotuzumab ozogamicin is due to the binding of the ADC to CD22-expressing tumour cells, followed by internalisation of the ADC-CD22 complex, and the intracellular release of N-acetyl-gamma-calicheamicin dimethylhydrazide via hydrolytic cleavage of the linker. Activation of N-acetyl-gamma-calicheamicin dimethylhydrazide induces double-strand DNA breaks, subsequently inducing cell cycle arrest and apoptotic cell death.

Pharmacodynamics

Pharmacodynamic Effects

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

Cardiac Electrophysiology

Based on a pharmacokinetic exposure-response analysis in 250 patients with relapsed or refractory ALL or other haematologic malignancies who received 1.8 mg/m^2/cycle inotuzumab ozogamicin 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) of a 21- to 28-day cycle or 1.8 mg/m^2/cycle administered once every 4 weeks, respectively, the median QT interval corrected for heart rate using Fridericia's formula (QTcF) increased by 2.53 milliseconds (msec) from baseline (97.5th percentile: 4.92 msec) at the average maximum observed concentration (C_{max}) estimated for patients with relapsed or refractory ALL (371 ng/mL) and by 3.87 msec from baseline (97.5th percentile: 7.54 msec) at a 1.5 times higher average C_{max} (569 ng/mL).

In a randomised clinical study in patients with relapsed or refractory ALL (B1931022), increases in QTcF of ≥60 msec from baseline were measured in 4/162 (3%) patients in the BESPONSA arm and 3/124 (2%) patients in the Investigator's choice of chemotherapy arm. Increases in QTcF of >500 msec were observed in none of the patients in the BESPONSA arm and 1/124 (1%) patients in the Investigator's choice of chemotherapy arm. Mean (90% confidence interval [CI]) maximum QTcF changes from baseline were 16.5 msec (14.3-18.7) in the BESPONSA arm and 10.8 msec (8.0-13.6) in the Investigator's choice of chemotherapy arm. Central tendency analysis of the QTcF interval changes from baseline showed that the highest upper bound of the 2-sided 90% CI for QTcF was 21.1 msec (observed at Cycle 4/Day 1/1 hour) in the BESPONSA arm and 21.2 msec (observed at Cycle 2/Day 1/1 hour) in the Investigator's choice of chemotherapy arm (see Section 4.4 Special warnings and precautions for use, QT Interval Prolongation).

Clinical trials

Patients with Relapsed or Refractory ALL who have received 1 or 2 Prior Treatment Regimens for ALL – Study B1931022

The safety and efficacy of BESPONSA in patients with relapsed or refractory ALL were evaluated in a randomised, open-label, international, multicentre, Phase 3 study (B1931022). Eligible patients 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. Table 1 in Section 4.2 Dose and method of administration shows the dosing regimen used to treat patients.

Among all 326 patients randomised to the study, 164 patients received BESPONSA and 162 patients received Investigator's choice of chemotherapy.

Among the initial 218 patients who were randomised to receive BESPONSA (N=109) or Investigator's choice of chemotherapy including fludarabine + cytarabine + granulocyte colony-stimulating factor (FLAG), mitoxantrone + cytarabine (MXN/Ara-C), or high dose cytarabine (HIDAC) (N=109), and who were assessed for complete remission/complete remission with incomplete haematologic recovery (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 (85%) patients had Philadelphia chromosome-negative ALL, 133 (61%) patients had a duration of first remission <12 months, and 39 (18%) patients had undergone a haematopoietic stem cell transplant (HSCT) prior to receiving BESPONSA or Investigator's choice of chemotherapy.

Among all 326 patients who were randomised 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. The two treatment groups were generally balanced with respect to the baseline demographics and disease characteristics.

All evaluable patients had B-cell precursor ALL that expressed CD22, with ≥90% of evaluable patients exhibiting ≥70% leukaemic blast CD22 positivity prior to treatment, as assessed by flow cytometry performed at a central laboratory.

The primary endpoints were CR/CRi, assessed by a blinded independent EAC, and overall survival (OS). The secondary endpoints included minimal residual disease (MRD) negativity, duration of remission (DoR), HSCT rate, and progression-free survival (PFS). CR/CRi, MRD, and DoR were analysed in the initial 218 randomised patients and OS, PFS, and HSCT rate were analysed in all 326 randomised patients.

Table 7 shows the efficacy results for CR/CRi, MRD-negativity, and DoR in the initial 218 patients from this study. Table 8 shows the efficacy results for OS, PFS, and HSCT rate in all 326 patients from this study.

Table 7. Efficacy Results for CR/CRi, MRD-Negativity, and DoR in Initial 218 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]
p-value[c]	0.0011		<0.0001		<0.0001	
MRD-negativity[d]						
n	35	6	34	3	69	9
Rate[e] (%) [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]
p-value[c]	<0.0001		0.0034		<0.0001	
DoR[f]						
n	39	18	45	14	84	32

Table 7. Efficacy Results for CR/CRi, MRD-Negativity, and DoR in Initial 218 Patients with Relapsed or Refractory B-Cell Precursor ALL who received BESPONSA or Investigator's Choice of Chemotherapy (FLAG, MXN/Ara-C, or HIDAC)

Median (mo) [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]
HR[g] [95% CI]	0.352 [0.152-0.813]		0.401 [0.181-0.887]		0.502 [0.303-0.832]	
p-value[h]	0.0058		0.0104		0.0031	

Based on 02 October 2014 cutoff date for CR/CRi and MRD-negativity and 08 March 2016 cutoff date for DoR.

Abbreviations: ALL= acute lymphoblastic leukaemia; CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete haematologic recovery; DoR=duration of remission; EAC=Endpoint Adjudication Committee; FLAG=fludarabine + cytarabine + granulocyte colony-stimulating factor; HIDAC=high-dose cytarabine; HR=hazard ratio; 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 leukaemic blasts, full recovery of peripheral blood counts (platelets $\geq 100 \times 10^9$/L and absolute neutrophil counts [ANC] $\geq 1 \times 10^9$/L) and resolution of any extramedullary disease.

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

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

[d] MRD-negativity was defined by flow cytometry as leukaemic cells comprising $< 1 \times 10^{-4}$ (<0.01%) of bone marrow nucleated cells.

[e] 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.

[f] 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.

[g] Estimated using stratified Cox regression.

[h] 1-sided p-value using stratified log-rank test.

Table 8. Efficacy Results for OS, PFS, and HSCT Rate in All 326 Patients with Relapsed or Refractory B-Cell Precursor ALL who received BESPONSA or Investigator's Choice of Chemotherapy (FLAG, MXN/Ara-C, or HIDAC)

	BESPONSA (N=164)	**HIDAC, FLAG, or MXN/Ara-C (N=162)**
OS		
Median (mo) [95% CI]	7.7 [6.0-9.2]	6.2 [4.7-8.3]
HR[a] [97.5% CI]	0.751 [0.568-0.993]	
p-value[a]	0.0105	
PFS		
Median (mo) [95% CI]	5.0 [3.7-5.6]	1.8 [1.5-2.2]
HR[b] [97.5% CI]	0.452 [0.336-0.609]	
p-value[a]	<0.0001	
HSCT Rate		
n (%) [95% CI]	79 (48.2) [40.3-56.1]	36 (22.2) [16.1-29.4]

Table 7. Efficacy Results for CR/CRi, MRD-Negativity, and DoR in Initial 218 Patients with Relapsed or Refractory B-Cell Precursor ALL who received BESPONSA or Investigator's Choice of Chemotherapy (FLAG, MXN/Ara-C, or HIDAC)

p-value[c]	<0.0001

Based on 08 March 2016 cutoff date for PFS and 04 January 2017 last subject last visit date for OS and HSCT.
Abbreviations: ALL=acute lymphoblastic leukaemia; CI=confidence interval; FLAG=fludarabine + cytarabine + granulocyte colony-stimulating factor; HIDAC=high-dose cytarabine; HR=hazard ratio; HSCT=haematopoietic stem cell transplant; mo=months; MXN/AraC=mitoxantrone + cytarabine; N/n=number of patients; OS=overall survival; PFS=progression-free survival.
[a] 1-sided p-value using stratified log-rank test.
[b] Estimated using stratified Cox regression.
[c] 1-sided p-value using Chi-squared test.

Among the initial 218 randomised patients, 88/109 achieved CR/CRi as per EAC in the BESPONSA arm (64/88 [73%] in Cycle 1; 21/88 [24%] in Cycle 2) and 32/109 achieved CR/CRi as per EAC in the Investigator's choice of chemotherapy arm (29/32 [91%] in Cycle 1; 1/32 [3%] in Cycle 2).

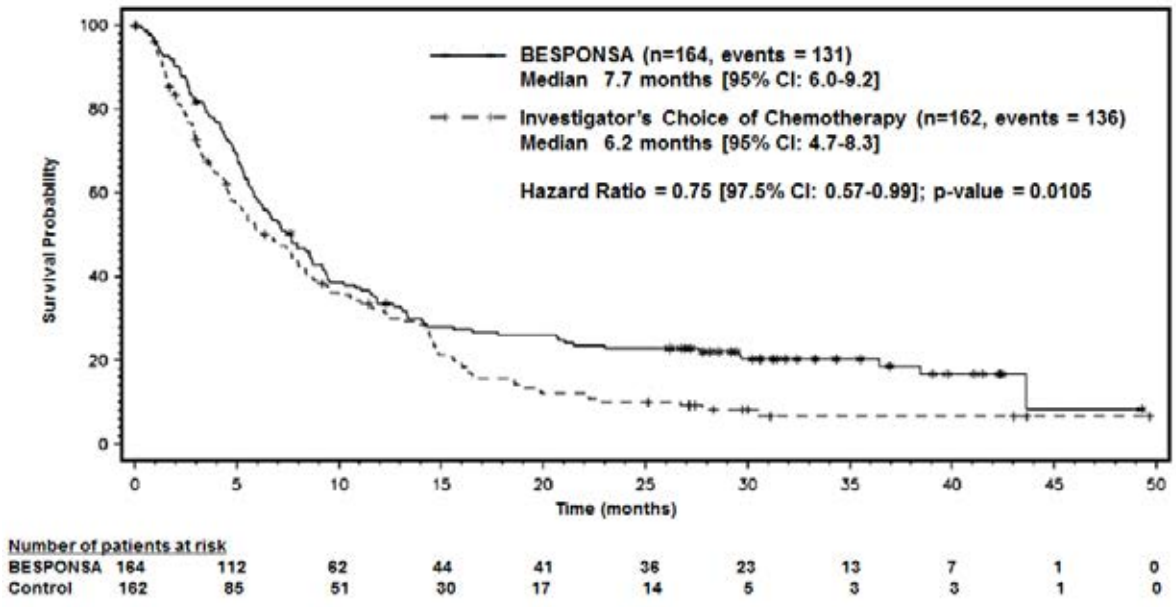
CR/CRi, MRD, and DoR results in the initial 218 randomised patients were consistent with those seen in all 326 randomised patients.

Among the 164 patients randomised to the BESPONSA arm, 62 patients achieved and remained in CR/CRi and proceeded directly to HSCT with a median of 4.9 weeks (range: 3.4 - 7.1 weeks) between the last dose of BESPONSA and proceeding to HSCT.

A total of 79/164 (48%) patients in the BESPONSA arm and 36/162 (22%) patients in the Investigator's choice of chemotherapy arm had a follow-up HSCT. This included 70 and 18 patients in the BESPONSA arm and Investigator's choice of chemotherapy arm, respectively, who proceeded directly to HSCT.

Figure 1 shows the analysis of overall survival (OS) (hazard ratio: 0.75; p=0.0105). Median OS was 7.7 months in the BESPONSA arm and 6.2 months in the Investigator's choice of chemotherapy arm. Among all 326 randomised patients, the survival probability at 24 months was 22.8% in the BESPONSA arm and 10.0% in the Investigator's choice of chemotherapy arm. 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)



Based on 04 January 2017 last subject last visit date.

Patient reported outcomes were measured using the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30). BESPONSA resulted in significantly better estimated mean postbaseline scores (BESPONSA and Investigator's choice of chemotherapy, respectively) in physical functioning (75.0 versus 68.1; p=0.0139), role functioning (64.7 versus 53.4; p=0.0065), social functioning (68.1 versus 59.8; p=0.0336), and appetite loss (17.6 versus 26.3; p=0.0193) compared to Investigator's choice of chemotherapy.

5.2 Pharmacokinetic properties

In patients with relapsed or refractory ALL, steady-state exposure was achieved by Cycle 4. The mean C_{max} of inotuzumab ozogamicin was 308 ng/mL. The mean simulated total area under the concentration-time curve (AUC) per cycle was 100,000 ngŸh/mL.

Distribution

In vitro, the binding of N-acetyl-gamma-calicheamicin dimethylhydrazide to human plasma proteins is approximately 97%. *In vitro*, N-acetyl-gamma-calicheamicin dimethylhydrazide is a substrate of P-glycoprotein (P-gp). In humans, the total volume of distribution of inotuzumab ozogamicin was approximately 12 L.

Metabolism

In vitro, N-acetyl-gamma-calicheamicin dimethylhydrazide was primarily metabolised via nonenzymatic reduction. In humans, N-acetyl-gamma-calicheamicin dimethylhydrazide serum levels were typically below the limit of quantitation.

Excretion

Inotuzumab ozogamicin pharmacokinetics were well characterised by a 2-compartment model with linear and time-dependent clearance components. In 234 patients with relapsed or refractory ALL, the clearance of inotuzumab ozogamicin at steady state was 0.0333 L/h and the terminal half-life ($t_{½}$) was 12.3 days. Following administration of multiple doses, a 5.3 times accumulation of inotuzumab ozogamicin was predicted by Cycle 4.

Based on a population pharmacokinetic analysis in 765 patients, body surface area was found to significantly affect inotuzumab ozogamicin disposition. The dose of BESPONSA is administered based on body surface area (see Section 4.2 Dose and method of administration).

Special Populations

Age, Race and Gender

Based on a population pharmacokinetic analysis, age, race, and gender did not significantly affect inotuzumab ozogamicin disposition.

Hepatic Impairment

No formal pharmacokinetic studies of BESPONSA have been conducted in patients with hepatic impairment.

Based on a population pharmacokinetic analysis in 765 patients, 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 ≤ upper limit of normal [ULN] and aspartate aminotransferase [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 Section 4.4 Special warnings and precautions for use, Use in Hepatic Impairment). In 3 patients with hepatic impairment defined by NCI ODWG category C (total bilirubin >1.5-3 × ULN and AST any level) and 1 patient with NCI ODWG category D (total bilirubin >3 × ULN and AST any level), inotuzumab ozogamicin clearance did not appear to be reduced.

Renal Impairment

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

Based on a population pharmacokinetic analysis in 765 patients, the clearance of inotuzumab ozogamicin in patients with mild renal impairment (creatinine clearance [CLcr] 60-89 mL/min; n=237), moderate renal impairment (CLcr 30-59 mL/min; n=122), or severe renal impairment (CLcr 15-29 mL/min; n=4) was similar to patients with normal renal function

(CLcr ≥90 mL/min; n=402) (see Section 4.4 Special warnings and precautions for use, Use in Renal Impairment). The safety and efficacy of inotuzumab ozogamicin have not been studied in patients with end stage renal disease.

5.3 Preclinical safety data

Genotoxicity

Inotuzumab ozogamicin was clastogenic *in vivo* in the bone marrow of male mice that received single intravenous 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 an *in vitro* bacterial reverse mutation (Ames) assay.

Carcinogenicity

Formal carcinogenicity studies have not been conducted with inotuzumab ozogamicin. In intravenous 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 0.1 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 4 times the human clinical exposure based on AUC) at the end of the 26-week dosing period.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each vial contains the following inactive ingredients:

- trometamol
- sucrose
- polysorbate 80
- sodium chloride.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

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.

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.

6.4 Special precautions for storage

Store unopened vials in the original carton at 2-8°C (Refrigerate. Do not freeze) and protect from light until time of use.

Table 9 shows the storage times and conditions for reconstitution, dilution, and administration of BESPONSA.

Table 9. Storage Times and Conditions for Reconstituted and Diluted BESPONSA Solution

← Maximum time from reconstitution through end of administration ≤ 8 hours[a] →		
Reconstituted Solution	**Diluted Solution**	
	After Start of Dilution	**Administration**
Use reconstituted solution immediately or after being refrigerated (2-8°C) for up to 4 hours. **PROTECT FROM LIGHT**. **DO NOT FREEZE.**	Use diluted solution immediately or after storage at room temperature (20-25°C) or being 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**. **DO NOT FREEZE.**	If the diluted solution is refrigerated (2-8°C), bring it to room temperature (20-25°C) for approximately 1 hour prior to administration. Administer diluted solution as a 1-hour infusion at a rate of 50 mL/h at room temperature (20-25°C). **PROTECT FROM LIGHT**.

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

6.5 Nature and contents of container

Each carton contains 1 single-use vial containing 1 mg of sterile, preservative free, white to off-white lyophilised cake or powder for injection.

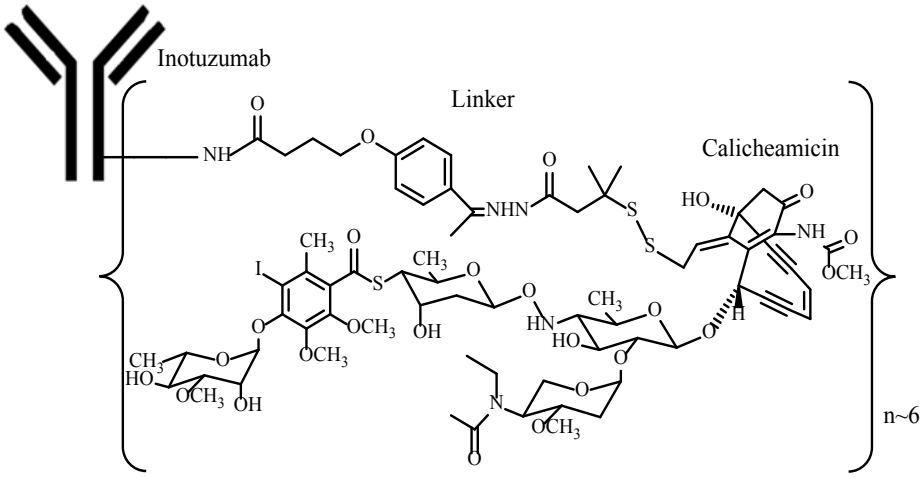
The container is a Type I amber glass vial with chlorobutyl rubber stoppers and crimp seals with a flip off cap.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



Chemical Name: Conjugate of humanised immunoglobulin class G subtype 4 (IgG4) monoclonal antibody with N-acetyl-calicheamicin (via a linker) with an average loading of 6 moles of calicheamicin derivative/mole of antibody.

Molecular weight: approximately 160 kDa with 6 calicheamicin derivatives.

CAS Number

CAS Registry Number: activated calicheamicin derivative: 174885-02-0

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Pfizer Australia Pty Ltd
38-42 Wharf Road
WEST RYDE NSW 2114
Toll Free Number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

17 May 2018

10. DATE OF REVISION

Not applicable.

Ò Registered trademark