Inotuzumab ozogamicin Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
Monotherapy for the treatment of adults with relapsed or refractory CD22- positive B cell precursor acute lymphoblastic leukaemia (ALL). Adult patients with Philadelphia chromosome positive (Ph+) relapsed or refractory B cell precursor ALL should have failed treatment with at least 1 tyrosine kinase inhibitor (TKI).	C91	00537a	ODMS 01/05/2019

**If the reimbursement status is not defined[i], the indication has yet to be assessed through the formal HSE reimbursement process.*

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Note:

- For patients proceeding to haematopoietic stem cell transplant (HSCT), the recommended duration of treatment is 2 cycles.
- A third cycle may be considered for those patients who do not achieve a complete remission (CR) or complete remission with incomplete haematological recovery (CRi) and minimal residual disease (MRD) negativity after 2 cycles.
- For patients not proceeding to HSCT, additional cycles of treatment, up to a maximum of 6 cycles, may be administered.
- Patients who do not achieve a CR/CRi within 3 cycles should discontinue treatment.

- For the **first** cycle, the recommended total dose of inotuzumab ozogamicin for all patients is 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) of a 21 day cycle.
    - Cycle 1 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 inotuzumab ozogamicin is 1.5 mg/m^2 per cycle given as 3 divided doses on Days 1 (0.5 mg/m^2), Day 8 (0.5 mg/m^2), and Day 15 (0.5 mg/m^2) for patients who achieve a complete remission (CR) or complete remission with incomplete haematological recovery (CRi) over a 28 day cycle
    - If patients do not achieve a CR/CRI the recommended dose of inotuzumab ozogamicin is 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)

Cycle 1

Day	Drug	Dose	Route	Diluent & Rate	Cycle (21 days)[a]
1	inotuzumab ozogamicin	0.8mg/m^2	IV	50ml NaCl 0.9% over 60 minutes	1
8[b], 15[b]	Inotuzumab ozogamicin	0.5mg/m^2	IV	50ml NaCl 0.9% over 60 minutes	1
For patients with circulating lymphoblasts cytoreduction with a combination of hydroxyurea, steroids, and/or vincristine to a peripheral blast count ≤ 10,000/mm3 is recommended prior to the first dose.					
[a]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					
[b]Doses on days 8 and 15 may be varied by ±2 days (maintain a minimum of 6 days between doses)					

Cycle 2 and subsequent cycles depending on response to treatment

- **Patients who have achieved a CR or CRi**

Day	Drug	Dose	Route	Diluent & Rate	Cycle (28 days)
1, 8[a], 15[a]	Inotuzumab ozogamicin	0.5mg/m^2	IV	50ml NaCl 0.9% over 60 minutes	2 onward
[a]Doses on days 8 and 15 may be varied by ±2 days (maintain a minimum of 6 days between doses)					

- **Patients who have not achieved a CR or CRi**

Day	Drug	Dose	Route	Diluent & Rate	Cycle (28 days)
1	Inotuzumab ozogamicin	0.8mg/m^2	IV	50ml NaCl 0.9% over 60 minutes	2 onward
8[a], 15[a]	Inotuzumab ozogamicin	0.5mg/m^2	IV	50ml NaCl 0.9% over 60 minutes	2 onward
[a]Doses on days 8 and 15 may be varied by ±2 days (maintain a minimum of 6 days between doses)					

ELIGIBILTY:

- Indications as above
- Relapsed or refractory CD22-positive ALL due to receive either salvage 1 or salvage 2 therapy. Ph+ ALL patients must have failed treatment with at least 1 second generation tyrosine kinase inhibitor
- ECOG 0-2
- Bone marrow involvement with ≥ 5% lymphoblasts
- Adequate liver function, including total serum bilirubin ≤1.5 x ULN unless the patient has documented Gilbert syndrome, and aspartate and alanine aminotransferase (AST and ALT) ≤2.5 x ULN.
- If organ function abnormalities are considered due to tumour, total serum bilirubin must be ≤2 x ULN

- Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or any serum creatinine level associated with a measured or calculated creatinine clearance of ≥40 mL/min;

EXCLUSIONS:

- 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).
- Active central nervous system (CNS) leukaemia
- Isolated extramedullary disease
- Known infection with human immunodeficiency virus (HIV) or current chronic infection with hepatitis B virus (HBsAg positive) or hepatitis C virus (anti-HCV positive)
- Prior allogeneic hematopoietic stem cell transplant (HSCT) or other anti-CD22 immunotherapy ≤ 4 months before randomization. Patients must not have > grade 2 acute GvHD, or either moderate or severe limited chronic GvHD, or extensive GvHD of any severity
- Peripheral lymphoblasts > 10,000 /microlitre
  For patients with circulating lymphoblasts, cytoreduction with a combination of hydroxyurea, steroids, and/or vincristine to a peripheral blast count ≤ 10,000/microlitre

- QTcF > 470 msec (based on the average of 3 consecutive ECGs)

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies

TESTS:

Baseline tests:

- Baseline CD22 positivity of > 0% using a validated and sensitive assay
- FBC, renal and liver profile
- Coagulation screen
- Uric acid
- Urinalysis
- Cardiac Function : ECG, LVEF (ECHO or MUGA)
- CSF imunophentyping to exclude CNS involvement
- Virology screen -Hepatitis B (HBsAg, HBcoreAb) & C, HIV.
  *See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation
- Pregnancy test

Regular tests:

- Liver profile (including ALK, AST, Bilirubin and Alkaline Phosphatase) prior and following each dose of inotuzumab ozogamicin
- FBC, renal profile prior to each cycle
- Uric acid

- Coagulation screen
- Cardiac Function as clinically indicated
- Bone marrow as clinically appropriate

Disease monitoring:
Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- Management of some adverse drug reactions may require dosing interruptions and/or dose reductions, or permanent discontinuation of inotuzumab ozogamicin.
- If the dose is reduced due to inotuzumab ozogamicin-related toxicity, the dose should not be re-escalated.
- Inotuzumab ozogamicin 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-haematological toxicities

Haematological:

Table 1: Dose modification of inotuzumab ozogamicin in haematological toxicity at the start of a cycle – i.e. Day 1

ANC ($x10^9$ /L)		[a]Platelets ($x10^9$ /L)	Dose
≥1.0	or	≥50	100%
<1.0	and/or	<50	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 × 10^9 /L and platelet count recovers to ≥ 50 × 10^9 /L **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 inotuzumab ozogamicin-related toxicity).

[a] Platelet count used for dosing must be independent of blood transfusion

Renal and Hepatic Impairment:

Table 2: Dose modification of inotuzumab ozogamicin in renal and hepatic impairment

Renal Impairment		Hepatic Impairment			
CrCl (ml/min)	Dose	Total Bilirubin (micromol/L)		AST/ALT	Dose
≥15	No adjustment to the starting dose				
<15	The safety and efficacy of inotuzumab	≤ 1.5 x ULN	And	≤ 2.5 × ULN	100% dose

	ozogamicin have not been studied in patients with end-stage renal disease.	> 1.5 × ULN	And	> 2.5 × ULN	Hold until recovery* Permanently discontinue treatment if total bilirubin does not recover to ≤ 1.5 × ULN or AST/ALT does not recover to ≤ 2.5 × ULN.
* Unless due to Gilbert's syndrome or haemolysis					

See table 4 for dose modification of treatment-induced hepatotoxity

Management of adverse events:

Table 3: Dose Modification of inotuzumab ozogamicin for Adverse Events

Adverse reactions	Recommended dose modification
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.
Grade ≥ 2[a] non-haematological toxicity (inotuzumab ozogamicin-related)	Interrupt treatment until recovery to Grade 1 or pre-treatment grade levels prior to each dose.

[a] NCI CTCAE version 3.0.

Treatment related hepatotoxicity

Table 4: Dose modifications of inotuzumab ozogamicin in treatment related hepatoxicity

Adverse reactions	Recommended dose modification
Venoocclusive disease/sinusoidal obstruction syndrome. (VOD/SOS) or other severe liver toxicity	Permanently discontinue treatment
Total bilirubin > 1.5 × ULN and AST/ALT > 2.5 × ULN	Hold until recovery* Permanently discontinue treatment if total bilirubin does not recover to ≤ 1.5 × ULN or AST/ALT does not recover to ≤ 2.5 × ULN.
* Unless due to Gilbert's syndrome or haemolysis	

Management of dose interruptions

Table 5: Dose modifications depending on duration of dosing interruption due to toxicity

Duration of dosing interruption due to toxicity	Recommended dose modification
< 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.
> 28 days	Consider permanent discontinuation of inotuzumab ozogamicin.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Moderate (**Refer to local policy).**

PREMEDICATIONS: Premedication consisting of an anti-pyretic, corticosteroid and an anti-histamine

should always be administered before each infusion of inotuzumab ozogamicin

Table 6: Suggested pre-medications prior to inotuzumab ozogamicin ozogamicin infusion:

Drugs	Dose	Route
Paracetamol	1g	PO 60minutes prior to inotuzumab ozogamicin infusion
Chlorphenamine	10mg	IV bolus 60minutes prior to inotuzumab ozogamicin infusion
Hydrocortisone	100 mg	IV bolus 60 minutes prior to infusion

OTHER SUPPORTIVE CARE:

- Tumour lysis syndrome prophylaxis **(Refer to local policy)**
- Proton pump Inhibitor**(Refer to local policy)**
- Mouth care **(Refer to local policy).**
- G-CSF **(Refer to local policy)**
- PJP prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis **(Refer to local policy)**
- Anti-viral prophylaxi**s (Refer to local policy)**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Hepatotoxicity, including venoocclusive liver disease/sinusoidal obstruction syndrome (VOD/SOS)** Hepatotoxicity, including severe, life-threatening, and sometimes fatal hepatic VOD/SOS, was reported in patients with relapsed or refractory ALL receiving inotuzumab ozogamicin. This risk was most marked in patients who underwent subsequent HSCT.
  In the following subgroups, the reported frequency of VOD/SOS post-HSCT was ≥ 50%:
  - Patients who received a HSCT conditioning regimen containing 2 alkylating agents;
  - Patients aged ≥ 65 years; and
  - Patients with a serum bilirubin ≥ ULN prior to HSCT.

  The use of HSCT conditioning regimens containing 2 alkylating agents should be avoided. The benefit/risk should be carefully considered before administering inotuzumab ozogamicin to patients in whom the future use of HSCT conditioning regimens containing 2 alkylating agents is likely unavoidable.
  In patients in whom the serum bilirubin is ≥ ULN prior to HSCT, HSCT post inotuzumab ozogamicin treatment should only be undertaken after careful consideration of the benefit/risk. If these patients do proceed to HSCT, signs and symptoms of VOD/SOS should be monitored closely.
  Other patient factors that appear to be associated with an increased risk of VOD/SOS after HSCT include a prior HSCT, age ≥ 55 years, a history of liver disease and/or hepatitis before treatment, later salvage lines, and a greater number of treatment cycles.
  Careful consideration is required before administering inotuzumab ozogamicin to patients who have had a prior HSCT.
  Patients with a history of liver disease should be carefully evaluated (e.g., ultrasound scan, viral hepatitis testing) prior to treatment with inotuzumab ozogamicin to exclude serious ongoing

hepatic disease.

For patients proceeding to HSCT, the recommended duration of treatment is 2 cycles, with a maximum of 3 cycles, to reduce the risk of VOD/ SOS.

- **Myelosuppression/cytopenias:** In patients receiving inotuzumab ozogamicin, neutropenia, thrombocytopenia, anaemia, leukopenia, febrile neutropenia, lymphopenia, and pancytopenia, some of which were life-threatening, have been reported.
- **Infusion related reactions:** In patients receiving inotuzumab ozogamicin, infusion related reactions were reported. Patients should be monitored 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, or breathing problems. If an infusion related reaction occurs, the infusion should be interrupted and appropriate medical management should be instituted. Depending on the severity of the infusion related reaction, discontinuation of the infusion or administration of steroids and antihistamines should be considered. For severe or life-threatening infusion reactions, treatment should be permanently discontinued.
- **Tumor lysis syndrome (TLS):** In patients receiving inotuzumab ozogamicin, TLS, which may be life-threatening or fatal, was reported. Pre-medication to reduce uric acid levels and hydration is recommended prior to dosing for patients with a high tumour burden
- **QT interval prolongation**: In patients receiving inotuzumab ozogamicin, QT interval prolongation was observed. Inotuzumab ozogamicin should be administered with caution in patients who have a history of, or predisposition to QT interval prolongation, who are taking medicinal products that are known to prolong QT interval and in patients with electrolyte disturbances.
- **Hepatitis B Reactivation:** All patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with lamivudine 100 mg/day orally, for the entire duration of chemotherapy and for six months afterwards. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to stopping chemotherapy.
- **Immunisations:** The safety of immunisation with live viral vaccines during or following inotuzumab ozogamicin therapy has not been studied. Vaccination with live viral vaccines is not recommended for at least 2 weeks prior to the start of inotuzumab ozogamicin treatment, during treatment, and until recovery of B lymphocytes following the last treatment cycle.

DRUG INTERACTIONS

- In patients receiving inotuzumab ozogamicin, QT interval prolongation has been observed so the concomitant use of inotuzumab ozogamicin with medicinal products known to prolong QT interval or to induce Torsades de Pointes should be carefully considered. The QT interval should be monitored in case of combinations of such medicinal products
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Inotuzumab ozogamicin L01XC26

REFERENCES:

1 Kantarjian et al. Inotuzumab ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia N Engl J Med 2016;375:740-53

2 Besponsa®Summary of product characteristics accessed October 2018 available at https://www.ema.europa.eu/documents/product-information/besponsa-epar-product-information_en.pdf
3 CCLG guideline on the management of chemotherapy induced nausea and vomiting March 2018 https://www.piernetwork.org/uploads/4/7/8/1/47810883/cclg_cinv_guideline_march_2018.pdf

Version	Date	Amendment	Approved By
1	10/04/2019		Dr. Derville O'Shea

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/