Idelalisib and RiTUXimab Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
In combination with riTUXimab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy	C91	00389a	Idelalisib: CDS riTUXimab: Hospital
In combination with riTUXimab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) as first line treatment in the presence of 17p deletion or *TP53* mutation in patients who are not eligible for any other therapies	C91	00389b	Idelalisib: CDS riTUXimab: Hospital

**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.

Idelalisib 150mg is taken orally, twice daily and treatment is continued until disease progression or unacceptable toxicity develops.
RiTUXimab is administered as 375mg/m^2 for the first dose, with 500mg/m^2 given every 2 weeks for 4 doses (Weeks 2,4,6 and 8) and then every 4 weeks for 3 doses (Weeks 12,16,and 20) for a total of 8 doses

Facilities to treat anaphylaxis MUST be present when riTUXimab therapy is administered.

Drug	Dose	Route	Diluent & Rate	Cycle
Idelalisib	150 mg BD	PO	N/A	Continuous
Tablets should be taken either with or without food				
If the patient misses a dose within 6 hours of the time it is usually taken, the patient should take missed dose as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 6 hours, the patient should not take the missed dose and should simply resume the usual dosing schedule.				
Idelalisib is available as 100mg and 150mg tablets				

Drug	Dose	Route	Diluent & Rate	Week
riTUXimab	375 mg/m^2	IV infusion[1] Observe post infusion[2]	250 ml 0.9% NaCl at a maximum rate of 400mg/hr[1,3]	0
riTUXimab	500 mg/m^2	IV infusion[1] Observe post infusion[2]	250 ml 0.9% NaCl at a maximum rate of 400mg/hr[1,3,4]	2,4,6,8,12,16 & 20

[1]The recommended initial rate for infusion is 50 mg/hr; after the first 30 minutes, it can be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
Subsequent infusions can be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30 minute intervals, to a maximum of 400 mg/hr. Development of an allergic reaction may require a slower infusion rate. See Hypersensitivity/Infusion reactions under Adverse Effects/Regimen Specific Complications below. Any deviation from the advised infusion rate should be noted in local policies

[2]Recommended Observation period: Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Any deviation should be noted in local policies.

[3]RiTUXimab should be diluted to a final concentration of 1-4mg/ml

[4] **Rapid rate infusion schedule[ii] See NCCP guidance here**
If patients did **not** experience a serious infusion related reaction with their first or subsequent infusions of a dose of riTUXimab administered over the standard infusion schedule, a more rapid infusion can be administered for second and subsequent infusions using the same concentration as in previous infusions.
Initiate at a rate of 20% of the total dose for the first 30 minutes and then 80% of the dose for the next 60 minutes (total infusion time of 90 minutes). If the more rapid infusion is tolerated, this infusion schedule can be used when administering subsequent infusions.
Patients who have clinically significant cardiovascular disease, including arrhythmias, or previous serious reactions to any prior biologic therapy or to riTUXimab, should not be administered the more rapid infusion.

ELIGIBILTY:

- Indications as above
- ECOG 0-3

EXCLUSIONS:

- Hypersensitivity to idelalisib, riTUXimab or any of the excipients

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profiles
- Cardiac function as clinically indicated
- Virology screen -Hepatitis B (HBsAg, HBcoreAb) & C, HIV.

*See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation

Regular tests:

- FBC and renal profile monthly
- Liver profile every 2 weeks for the first three months of treatment, then as clinically indicated.
- Cardiac function if clinically indicated

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.
- No dose reductions of riTUXimab are recommended

Haematological:

Table 1: Recommended dose modification of idelalisib in haematological toxicity

ANC ($x10^9$/L)	Dose
1 – 1.5	Maintain Idelalisib dosing
0.5 – 0.99	Maintain Idelalisib dosing. Monitor ANC at least weekly
<0.5	Interrupt Idelalisib dosing. Monitor ANC at least weekly until ANC ≥ 0.5 x 10^9/L , then may resume Idelalisib dosing at 100 mg twice daily

Renal and Hepatic Impairment:

Table 2: Recommended dose modification of idelalisib in renal and hepatic impairment

Renal Impairment	Hepatic Impairment
No dose adjustment is required for patients with mild, moderate, or severe renal impairment	No dose adjustment is required when initiating treatment with idelalisib in patients with mild or moderate hepatic impairment, but intensified monitoring of LFTS is recommended. There is insufficient data to make dose recommendations for patients with severe hepatic impairment. Therefore, caution is recommended when administering idelalisib in this population and intensified LFT monitoring for adverse effects is recommended

***See Table 3: Management of idelalisib in elevated liver transaminases**

Management of adverse events for idelalisib:

Table 3: Management of idelalisib in elevated liver transaminases

ALT/AST	Recommended management
>3.5 x ULN	Increase monitoring of LFTs including AST to weekly until the values fall to ≤ 3 x ULN.
First occurrence > 5 x ULN	Withhold treatment with idelalisib until ALT/AST ≤ 3 x ULN. Treatment can then be resumed at 100mg twice daily. If this event does not recur at 100mg twice daily, the dose can be increased to 150mg twice daily again, at the discretion of the prescribing Consultant.
Second occurrence >5 x ULN	Withhold idelalisib until ALT/AST ≤ 3 x ULN. Re-initiation at 100mg twice daily may be considered at the discretion of the prescribing Consultant.

Table 4: Management of idelalisib treatment related diarrhoea/colitis

Diarrhoea	Recommended management
Grade 1-2	No dose modification required Usually responsive to common antidiarrhoeal agents (Refer to Coutre et al for more detailed information (2))
Unresolved grade 2 and grade ≥3 Diarrhoea/colitiis	Initial management should include diagnostic testing to rule out infectious causes. After exclusion of infectious causes, initiation of budesonide oral or intravenous steroid therapy is recommended. The duration of treatment should be based on individual clinical response. Withhold treatment with idelalisib until diarrhoea/colitis resolved to ≤ Grade 1. Resume treatment at 100mg BD per clinical judgement.

Table 5: Dose Modification of idelalisib for Adverse Events

Adverse reactions	Recommended dose modification
Pneumonitis	Treatment with idelalisib must be withheld in the event of suspected pneumonitis. Once pneumonitis has resolved and if re-treatment is appropriate, resumption of treatment at 100 mg twice daily can be considered.
Grade ≥ 3 Rash	Withhold treatment until resolved to ≤ Grade 1. Resume treatment at 100mg BD. If rash does not recur, the dose may be escalated to 150mg BD at the discretion of the prescribing consultant.
Intestinal perforation	Discontinue treatment

Management of adverse events for riTUXimab :

Table 6: Dose modification schedule based on adverse events for riTUXimab

Adverse reactions	Recommended dose modification
Severe infusion related reaction (e.g dyspnoea, bronchospasm, hypotension or hypoxia) First occurrence Second occurrence	Interrupt infusion immediately. Evaluate for cytokine release/tumour lysis syndrome (appropriate laboratory tests) and pulmonary infiltration (chest x -ray). Infusion may be restarted on resolution of all symptoms, normalisation of laboratory values and chest x-ray findings at no more than one-half the previous rate. Consider coverage with steroids for those who are not already receiving steroids. Consider discontinuing treatment
Mild or moderate infusion-related reaction	Reduce rate of infusion. The infusion rate may be increased upon improvement of symptoms

SUPPORTIVE CARE:

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

PREMEDICATIONS:

Premedication consisting of an anti-pyretic and an anti-histamine should always be administered before each infusion of riTUXimab. Consider the inclusion of a glucocorticoid in patients not receiving glucocorticoid containing chemotherapy.

Table 7: Suggested pre-medications prior to riTUXimab infusion:

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

OTHER SUPPORTIVE CARE:

- Tumour cell lysis prophylaxis **(Refer to local policy)**
- PJP prophylaxis **(Refer to local policy)**
- Antiviral prophylaxis **(Refer to local policy)**
- Antifungal prophylaxis **(Refer to local policy)**
- Women of childbearing potential must use highly effective contraception while taking idelalisib and for 1 month after stopping treatment.
- Women using hormonal contraceptives should add a barrier method as a second form of contraception since it is currently unknown whether idelalisib may reduce the effectiveness of hormonal contraceptives

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

Idelalisib

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **Diarrhoea/Colitis**: Cases of severe drug-related colitis occurred relatively late (on average 6 months

after initiation of treatment but resolved within a few weeks with dose interruption and specific treatment. Please refer to Coutre SE, et al. "*Management of adverse events associated with idelalisib treatment-expert panel opinion*" (2) for detailed information on management. The recommended management is summarized in Table 2. There is very limited experience from the treatment of patients with a history of inflammatory bowel disease.

- **Pneumonitis**: Any patient presenting with pulmonary symptoms such as cough, dyspnoea, hypoxia, interstitial infiltrates on a radiologic examination or a decline in oxygen saturation by > 5% should be evaluated for pneumonitis. If pneumonitis is suspected, idelalisib should be interrupted until the cause is determined. Treatment with idelalisib must be discontinued for moderate or severe symptomatic pneumonitis, all patients should receive prophylaxis for PJP during treatment with idelalisib. This should be continued for 2-6 months after discontinuation of idelalisib. The duration of post-treatment prophylaxis should be based on clinical judgement.
- **CMV infection**: Regular clinical and lab monitoring for CMV infection is recommended in patients who are CMV-seropositive at the start of treatment with idelalisib or have other evidence of a history of CMV infection. Patients with CMV viraemia even without signs of CMV infection should be treated with appropriate anti-CMV therapy. For patients with evidence of CMV viraemia and clinical signs of CMV infection, treatment with idelalisib should be stopped. Idelalisib may be restarted if the infection has resolved and the benefits of resuming are judged to outweigh the risks. If re-started, pre-emptive CMV therapy should be considered.
- Cases of progressive multifocal leukoencephalopathy (PML) have been reported following the use of idelalisib within the context of prior- or concomitant immunosuppressive therapies that have been associated with PML. Physicians should consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioural signs or symptoms

RiTUXimab

- **Hypersensitivity/Infusion Reactions:** Close monitoring is required throughout the first infusion. (Refer to local policy). RiTUXimab can cause allergic type reactions during the IV infusion such as hypotension, wheezing, rash, flushing, pruritis, sneezing, cough, fever or faintness.
- **Severe Cytokine Release syndrome**: Usually occurs within 1 to 2 hours of initiating the first infusion. This syndrome may be associated with some features of cytokine release/tumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphatemia, acute renal failure, elevated lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and death.
    - Pulmonary interstitial infiltrates or oedema visible on chest x-ray may accompany acute respiratory failure.
    - For severe reactions, stop the infusion immediately and evaluate for tumour lysis syndrome and pulmonary infiltration. Aggressive symptomatic treatment is required. The infusion can be resumed at no more than one-half the previous rate once all symptoms have resolved, and laboratory values and chest x-ray findings have normalized.
- **Severe Mucocutaneous Reactions:** These include Steven Johnson syndrome and toxic epidermal necrolysis. Discontinue in patients who develop a severe mucocutaneous reaction. The safety of readministration has not been determined.
- **Cardiac Disorders:** Patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely.

- **Progressive multifocal leukoencephalopathy (PML):** Use of rituximab may be associated with an increased risk of PML. If a patient develops PML, the dosing of riTUXimab must be permanently discontinued.
- **Infections:** RiTUXimab should not be administered to patients with an active, severe infection. Caution should be exercised when considering the use of riTUXimab in patients with a history of recurring or chronic infections or with underlying conditions that may further predispose patients to serious infections. Consideration should be given to the use of antimicrobial prophylaxis.
- **Immunisations**:
  - The safety of immunisation with live viral vaccines following riTUXimab therapy has not been studied. Therefore vaccination with live virus vaccines is not recommended whilst on riTUXimab.
  - Patients treated with riTUXimab may receive non-live vaccinations
- **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 halting chemotherapy.

DRUG INTERACTIONS:

- Avoid co-administration with moderate or strong CYP3A inducers as this may result in reduced plasma concentrations of idelalisib.
- The primary metabolite of idelalisib, GS-563117, is a strong CYP3A4 inhibitor, and so the concomitant use of idelalisib with medicinal products metabolised by CYP3A may lead to increased serum concentrations of the other product.
- Antihypertensives: Additive effect of hypotension during riTUXimab infusion. Consider withholding antihypertensives 12 hours before and during rituximab infusion.
- There is a diminished response to vaccines and increased risk of infection with live vaccines. Vaccination with live virus vaccines is not recommended for patients on rituximab therapy.
- Patients with human anti-mouse antibody or human anti-chimeric antibody (HAMA/HACA) titres may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.
- Current drug interaction databases should be consulted for more information

ATC CODE:

Idelalisib	L01XX47
RiTUXimab	L01XC02

REFERENCES:

1. Furman, R et al; Idelalisib and rituximab in Relapsed Chronic Lymphocytic Leukaemia NEJM 2014; 370: 997 - 1007
2. Coutre SE, Barrientos JC et al. Management of adverse events associated with idelalisib treatment-expert panel opinion. Leukemia and Lymphoma 2015;56(10):2779-86
3. NCCP | RiTUXimab Rapid Infusion Rate Guidance | V1 2017 available at https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/sactguidance/guidance%20on%20rituximab%20rapid%20infusion%20rate.pdf

4. Idelalisib® Summary of product characteristics Accessed December 2018 Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003843/WC500175377.pdf
5. MabThera®Summary of Product Characteristics Accessed December 2018 Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000165/WC500025821.pdf

Version	Date	Amendment	Approved By
1	05/01/2017		Prof E Vandenberghe
2	11/02/2019	Updated to new NCCP template Inclusion of PML in idelalisib adverse events as per SmPC	Prof E Vandenberghe

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/

[ii] The rapid infusion is an unlicensed means of administration of riTUXimab for the indications described above, in Ireland. Patient's should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" means of administration has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.