Idelalisib and Ofatumumab Therapy

Please note ofatumumab is no longer commercially available from 01 March 2019.
New patients should not be started on this regimen

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
In combination with Ofatumumab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy	C91	00390a	Idelalisib: CDS Ofatumumab: hospital
In combination with Ofatumumab 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	00390b	Idelalisib: CDS Ofatumumab: hospital

**If the reimbursement status is not defined [1], 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.

The first infusion of ofatumumab is administered on Day 1 of week 1 at a dose of 300 mg and is then continued at a dose of 1,000 mg weekly for 7 doses (weeks 2-8), and then every 4 weeks for 4 doses (Total of 12 doses).

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

Drug	Dose	Route	Cycle
Idelalisib	150 mg BD	PO	Continuous
Tablets should be swallowed whole 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			

Day	Drug	Dose	Route	Diluent & Rate	Week
1	**Ofatumumab**	300mg	IV infusion Observe post infusion[1]	1000 ml 0.9% NaCl over 4.5 hours[2]	1
1	**Ofatumumab**	1000 mg	IV infusion Observe post infusion[1]	1000ml 0.9% NaCl over 4hours [3]	2,3,4,5,6,7,8, 12,16, 20 and 24
[1] Patients should be closely monitored during administration of ofatumumab for the onset of infusion reactions					
[2] ***First infusion*** The initial rate of the first infusion of ofatumumab should be 12 ml/hr. During infusion, the rate should be increased every 30 minutes to a maximum of 400 ml/hr (see Table 1 below)					
[3] ***Subsequent infusions*** If the first infusion has been completed without severe infusion related adverse drug reactions, the subsequent infusions can start at a rate of 25 ml/h and should be increased every 30 minutes up to a maximum of 400 ml/h r (see Table 1 below)					

Table 1: Infusion schedules for ofatumumab

Infusion 1 schedule for ofatumumab (Schedule for FIRST infusion)		**Infusion schedule for ofatumumab from infusion 2 onwards**	
Time after start of infusion (minutes)	**Infusion rate (ml/hour)**	**Time after start of infusion (minutes)**	**Infusion rate (ml/hour)**
0-30	12	0-30	**25**
31-60	25	31-60	**50**
61-90	50	61-90	100
91-120	100	91-120	200
121-150	200	121+	400
151-180	300		
180+	400		

ELIGIBILTY:

- Indications as above
- ECOG 0-3

EXCLUSIONS:

- Hypersensitivity to idelalisib, ofatumumab 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 if 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.

Haematological:

Table 2: Dose modification of idelalisib in haematological toxicity

ANC ($x10^9$/L)	Recommended dose modification
1 to 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 3: Recommended dose modification of idelalisib and ofatumumab in renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment
Idelalisib	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
Ofatumumab	No dose adjustment is recommended for mild to moderate renal impairment (creatinine clearance >30 ml/min)	No formal studies of ofatumumab in patients with hepatic impairment have been performed. However, patients with hepatic impairment are unlikely to require dose modification

***See Table 4: Management of idelalisib in elevated liver transaminases**

Management of adverse events:

Table 4: 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 5: 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 6: 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

Infusion related reactions with ofatumumab: Interrupt infusion for infusion related adverse reactions of any severity. Treatment can be resumed at the discretion of the treating physician. The following infusion rate modifications can be used as a guide (Table 1)

Table 7: Dose Modification schedule based on infusion related reactions for ofatumumab

Adverse reactions	Recommended dose modification
Severe infusion related reaction	The infusion should be interrupted and restarted at 12 ml/hour, when the patient's condition is stable. The infusion rate can continue to be increased according to standard procedures, according to physician discretion and patient tolerance (not to exceed increasing the rate every 30 minutes).
Mild or moderate infusion-related reaction	The infusion should be interrupted and restarted at half of the infusion rate at the time of interruption, when the patient's condition is stable. If the infusion rate had not been increased from the starting rate of 12 ml/hour prior to interrupting due to an adverse reaction, the infusion should be restarted at 12 ml/hour, the standard starting infusion rate. The infusion rate can continue to be increased according to standard procedures, according to physician discretion and patient tolerance (not to exceed increasing the rate every 30 minutes).

SUPPORTIVE CARE:

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

PREMEDICATIONS:

None usually required before idelalisib.

Patients should be pre-medicated 30 minutes to 2 hours prior to ofatumumab according to the following dosing schedule:

Table 8: Pre-medications required before ofatumumab infusion

[a]Previously untreated CLL	[b]Refractory CLL
Paracetamol 1000mg (or equivalent)	Paracetamol 1000mg (or equivalent)
Oral or intravenous antihistamine (diphenhydramine 50 mg or cetirizine 10 mg or equivalent	Oral or intravenous antihistamine (diphenhydramine 50 mg or cetirizine 10 mg or equivalent
Intravenous corticosteroid (prednisolone 50 mg or equivalent).	Intravenous corticosteroid (prednisolone 100 mg or equivalent).
[a]Following the first and second infusion, if the patient does not experience a severe adverse drug reaction (ADR), pre-medication with a corticosteroid for subsequent infusions may either be reduced or omitted, at the discretion of the physician.	
[b]If the second weekly infusion is completed without a severe adverse drug reaction the dose of the corticosteroid may be reduced for infusion numbers 3 through 8, at the discretion of the physician. Prior to the ninth infusion (first monthly infusion), patients should receive the full dose of premedication agents described above. If the ninth infusion is completed without a severe ADR, the dose may be reduced to the equivalent of 50 mg prednisolone for subsequent infusions at the discretion of the physician.	

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 5. 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 but 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

Ofatumumab

- **Infusion reactions**: Intravenous ofatumumab has been associated with infusion reactions. These reactions may result in temporary interruption or withdrawal of treatment. Pre-medications attenuate infusion reactions but these may still occur, predominantly during the first infusion. Infusion reactions may include, but are not limited to, anaphylactoid events, bronchospasm, cardiac events (eg. myocardial ischaemia / infarction, bradycardia), chills/rigors, cough, cytokine release syndrome, diarrhoea,

dyspnoea, fatigue, flushing, hypertension, hypotension, nausea, pain, pulmonary oedema, pruritus, pyrexia, rash, and urticaria. In rare cases, these reactions may lead to death. Even with pre-medication, severe reactions, including cytokine release syndrome, have been reported following use of ofatumumab. In cases of severe infusion reaction, the infusion of ofatumumab must be interrupted immediately and symptomatic treatment instituted. Infusion reactions occur more frequently on the first day of infusion and tend to decrease with subsequent infusions. Patients with a history of decreased pulmonary function may be at a greater risk for pulmonary complications from severe reactions and should be monitored closely during infusion of ofatumumab.

- **Progressive multifocal leukoencephalopathy (PML):** PML and death have been reported in CLL patients receiving cytotoxic pharmacotherapy, including ofatumumab. A diagnosis of PML should be considered in any ofatumumab patient who reports the new onset of or changes in pre-existing neurologic signs and symptoms. If a diagnosis of PML is suspected ofatumumab should be discontinued and referral to a neurologist should be considered.
- **Immunisations:** The safety of, and ability to generate a primary or anamnestic response to, immunisation with live attenuated or inactivated vaccines during treatment with ofatumumab has not been studied. The response to vaccination could be impaired when B cells are depleted. Due to the risk of infection, administration of live attenuated vaccines should be avoided during and after treatment with ofatumumab, until B cell counts are normalised. The risks and benefits of vaccinating patients during therapy with of ofatumumab should be considered.
- **Hepatitis B:** Hepatitis B virus (HBV) infection and reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, has occurred in patients treated with drugs classified as CD20-directed cytolytic antibodies, including ofatumumab. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in those who are hepatitis B core antibody (anti-HBc) positive but HBsAg negative. Reactivation has also occurred in patients who appear to have resolved hepatitis B infection (i.e. HBsAg negative, anti-HBc positive, and hepatitis B surface antibody [anti-HBs] positive).
- **Sodium content**: This medicinal product contains 34.8 mg sodium per 300 mg dose, 116 mg sodium per 1,000 mg dose and 232 mg sodium per 2,000 mg dose. This should be taken into consideration by patients on a controlled sodium diet.

- **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.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Idelalisib	L01XX47
Ofatumumab	L01XC10

REFERENCES:

1. Jones J, Wach M, Robak T, et al. Results of a phase III randomized, controlled study evaluating the efficacy and safety of idelalisib (IDELA) in combination with ofatumumab (OFA) for previously treated chronic lymphocytic leukemia (CLL) J Clin Oncol. 2015;33(Suppl):7023. http://meetinglibrary.asco.org/print/1998186
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. 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
4. Azerra®Summary of Product Characteristics Accessed December 2018 Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001131/WC500093091.pdf

Version	Date	Amendment	Approved By
1	05/01/2017		Prof E Vandenberghe
2	11/02/2019	Updated to new NCCP template. Updated idelalisib adverse events to include information on PML as per SmPC update	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/