Idelalisib Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment.	C82	00291a	CDS

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.

Drug	Dose	Route	Cycle
Idelalisib	150 mg twice daily	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 the 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.			

ELIGIBILITY:

- Indications as above
- ECOG 0-3

EXCLUSIONS:

- Hypersensitivity to idelalisib 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 as 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 1: Dose modification of idelalisib in haematological toxicity

ANC ($x10^9$/L)	Recommended dose
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 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:

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/colitis	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 twice daily 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 twice daily. If rash does not recur, the dose may be escalated to 150mg twice daily at the discretion of the prescribing consultant.
Intestinal perforation	Discontinue treatment

SUPPORTIVE CARE:

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

PREMEDICATIONS: None usually required

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

Idelalisib

- **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 summarised in Table 3. 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 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.
- **Pneumocystis jiroveci pneumonia (PJP):** 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.
- **Cytomegalovirus (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 interrupted. 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.
- **Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy **(Refer to local infectious disease policy).** These patients should be considered for assessment by hepatology.
- **Progressive multifocal leukoencephalopathy (PML):** 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.
- **Severe Cutaneous Reactions:** Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have occurred with idelalisib. Cases of SJS and TEN with fatal outcomes have been reported when idelalisib was administered concomitantly with other medicinal products associated with these syndromes. If SJS, TEN or DRESS is suspected, idelalisib should be interrupted and the patient assessed and treated accordingly. If a diagnosis of SJS, TEN, or DRESS is confirmed, idelalisib should be permanently discontinued.

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.

REFERENCES:

1. Gopal AK, Kahl BS, de Vos S, et al. PI3Kδdelta inhibition by idelalisib in patients with relapsed indolent lymphoma. NEJM 2014 ;370:1008-1018.
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 Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V4 2022. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
4. Idelalisib (Zydelig®) Summary of Product Characteristics. Accessed Mar 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/zydelig-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	05/01/2017		Prof Elisabeth Vandenberghe
2	11/02/2019	Updated to new NCCP template. Updated idelalisib adverse events to include information on PML as per SmPC update	Prof Elisabeth Vandenberghe
3	27/06/2022	Reviewed. Amended emetogenic potential and updated adverse effects.	Prof Elisabeth Vandenberghe

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.