IBRUTINIB

a) For treating CLL in adults who have had at least 1 prior therapy (NICE Jan 2017)
b) For treating CLL in adults who have a 17p or TP53 mutation, and in whom chemo-immunotherapy is unsuitable (NICE Jan 2017)
c) For relapsed mantle cell lymphoma
d) For adults with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy

No previous treatment with idelalisib, unless idelalisib had to be stopped within 6 months of its start solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression

Blueteq registration is required before treatment may start

All patients should be screened for hepatitis B virus before starting treatment with ibrutinib

Drugs/Dosage:

CLL or WM:

Ibrutinib	420mg (three capsules)	PO	once daily, continuous dosing

Mantle cell lymphoma:

Ibrutinib	560mg (four capsules)	PO	once daily, continuous dosing

Other Drugs: Consider allopurinol 300mg po od for the first four weeks; recommended for patients with a high tumour burden or elevated WBC
Loperamide as required, for management of any ibrutinib-associated diarrhoea

Frequency: once daily dosing continuously, until disease progression or unacceptable toxicity

Administration: Ibrutinib is available as 140mg capsules.
The capsules should be swallowed whole with water at approximately the same time each day.
Grapefruit and grapefruit juice, and Seville oranges, should be avoided while on ibrutinib.

Main Toxicities: myelosuppression; upper respiratory tract infection; diarrhoea; constipation; musculoskeletal pain; rash

Anti - emetics: mildly emetogenic (anti-emetic not usually required)

Regular Investigations:	FBC	every 4 weeks initially, increasing to 3 monthly in stable, responding patients
	LFTs	every 4 weeks initially, then as clinically indicated
	U&Es	every 4 weeks initially, then as clinically indicated

Comments: Ibrutinib should be withheld at least 3 to 7 days pre- and post-surgery, depending upon the type of surgery and the risk of bleeding.

Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use of ibrutinib in patients requiring any other medicines that inhibit platelet function may increase the risk of bleeding, and particular care should be taken if anticoagulant therapy is used.

Interactions: Avoid co-administration with CYP3A inducers (e.g. rifampicin, phenytoin, St John's wort, carbamazepine) as this may result in reduced plasma concentrations of ibrutinib.

Reason for Update: indication for WM added	Approved by Chair of Alliance TSSG: Dr A Laurie
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Prepared by: S Taylor	Checked by: C Tucker

Concomitant use of ibrutinib and strong or moderate CYP3A4 inhibitors can increase ibrutinib exposure and should be avoided if possible.

If a strong CYP3A4 inhibitor (e.g. clarithromycin, itraconazole, posaconazole) cannot be avoided, reduce the ibrutinib dose to 140 mg once daily or withhold for up to 7 days.
If a moderate CYP3A4 inhibitor (e.g. voriconazole, erythromycin, aprepitant, ciprofloxacin, diltiazem, fluconazole, verapamil, amiodarone) cannot be avoided, reduce the ibrutinib dose to 140 mg once daily for the duration of the inhibitor use.

Dose Modifications

Haematological Toxicity: Ibrutinib should be withheld if neutrophils < 1.0 x 10^9/l with infection or fever, or any grade 4 haematological toxicity (e.g. neutrophils < 0.5 x10^9/l or platelets < 25 x 10^9/l)
Once toxicity has resolved to Grade 1 or baseline, ibrutinib may be re-started, following the recommended dose modifications below:

Toxicity occurrence	CLL/WM dose modification after recovery	MCL dose modification after recovery
First	restart at 420 mg daily	restart at 560 mg daily
Second	restart at 280 mg daily	restart at 420 mg daily
Third	restart at 140 mg daily	restart at 280 mg daily
Fourth	discontinue ibrutinib	discontinue ibrutinib

Non-haematological Toxicities: Ibrutinib should be withheld for any new onset or worsening grade ≥ 3 non-haematological toxicity.
Once the toxicity has resolved to Grade 1 or baseline, ibrutinib may be re-started, again following the recommended dose modifications in the table above.

Renal Impairment: No dose adjustments are required for patients with CrCl > 30ml/minute.
There are no data in patients with CrCl < 30ml/min or patients on dialysis; administer to patients with CrCl < 30ml/min only if the benefit outweighs the risk, and monitor patients closely for signs of toxicity.

Hepatic Impairment: Ibrutinib is metabolized in the liver. When using ibrutinib in patients with mild or moderate hepatic impairment, monitor patients for signs of toxicity and follow dose modification guidance as needed.

Liver Function	Recommended dose of Ibrutinib
Mild hepatic impairment (Child-Pugh A)	280mg (two capsules) od
Moderate hepatic impairment (Child-Pugh B)	140mg (one capsule) od
Severe hepatic impairment (Child-Pugh C)	Not recommended

Patient Information: No Macmillan leaflet currently available.

References:
Byrd, J et al; NEJM 2014; 371: 213 – 223 (CLL)
Wang, M et al; NEJM 2013 ; 369 : 507 – 516
Treon, S et al ; NEJM 2015 ; 372 : 1430 – 1440 (WM)

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