

# Ibrutinib

## Indication

Treatment of relapsed or refractory Mantle Cell Lymphoma.

Treatment of Chronic Lymphocytic Leukaemia after at least one course of chemotherapy, or as first line treatment in patients with TP53 deletion not suitable for chemo-immunotherapy.

(Note: funding via CDF or individual request)

## ICD-10 codes

Codes 83.1 and 91.1

## Regimen details

### Mantle cell Lymphoma

Day	Drug	Dose	Route
1 – 30	Ibrutinib	560mg ( 4x 140mg capsules)	PO

### Chronic Lymphocytic Leukaemia

Day	Drug	Dose	Route
1 – 30	Ibrutinib	420mg (3 x 140mg capsules)	PO

## Cycle frequency

Every 30 days, continuously.

## Number of cycles

Continued until disease progression or unacceptable toxicity

## Administration

Ibrutinib is available as 140mg capsules.

Capsules should be taken once a day, at approximately the same time each day. They should be swallowed whole with water.

Seville oranges and grapefruit and grapefruit juice should be avoided whilst taking ibrutinib.

## Pre-medication

Nil

## Emetogenicity

This regimen has low emetic potential.

## Additional supportive medication

Allopurinol 300mg (100mg if creatinine clearance <20ml/min) OD for the first cycle

Loperamide if required

**Extravasation**

N/A

**Investigations – pre first cycle**

Investigation	Validity period
FBC	14 days
Clotting studies	14 days
U + E (including creatinine)	14 days
LFTs	14 days
Hepatitis core antibody and surface antigen	14 days
Hepatitis C antibody	14 days
HIV 1 and 2 status	1 month
CT staging of disease	2 months

Bone marrow biopsy (at consultant discretion)

**Investigations – pre subsequent cycles**

Investigation	Validity period
FBC	48 hours (monitor 4 weekly)
U + E (including creatinine)	48 hours (monitor 4 weekly)
LFTs	48 hours (monitor 4 weekly)

**Standard limits for administration to go ahead**If blood results not within range, authorisation to administer **must** be given by prescriber/consultant

Investigation	Limit
Neutrophils	$\geq 1.0 \times 10^9/L$
Platelets	$> 35 \times 10^9/L$
Creatinine clearance	$> 30\text{mL}/\text{min}$
Bilirubin	$< 1.5 \times \text{ULN}$

It is important to note that patients on ibrutinib will experience a worsening of lymphocytosis for the first 8-12 weeks and response cannot be assessed by drop in lymphocyte count.

**Dose modifications**

Toxicity occurrence	Ibrutinib dose (MCL)	Ibrutinib dose (CLL)
First	560mg OD	420mg OD
Second	420mg OD	280mg OD
Third	280mg OD	140mg OD
Fourth	Discontinue	Discontinue

- Haematological toxicity**

Withhold ibrutinib for any grade  $\geq 3$  neutropenia with infection or fever, or grade 4 haematological toxicity. Once toxicity resolved to grade 1 or baseline, re-start ibrutinib at the original dose. For further occurrences the dose should be reduced as per the dosing table above.

- Renal impairment**

No dose modifications required for patients with mild-moderate renal impairment ( $\text{CrCl} > 30\text{mL}/\text{min}$ ). There is no information on ibrutinib in patients with severe renal impairment or on dialysis; use with caution.

- Hepatic impairment**

Ibrutinib is metabolised by the liver. In hepatic impairment the dose should be modified as below:

Degree of hepatic impairment	Ibrutinib dose
Mild (Child-Pugh A)	280mg OD
Moderate (Child-Pugh B)	140mg OD
Severe (Child-Pugh C)	Not recommended

**Child Pugh Classification:**

Score	1	2	3
Bilirubin ( $\mu\text{mol/L}$ )	<34	34-50	>50
Albumin (g/L)	>35	28-35	<28
PT (s prolonged)	<4	4-6	>6
Encephalopathy	none	mild	marked
Ascites	none	mild	marked

The individual scores are summed and then grouped as:

- <7 = A
- 7-9 = B
- >9 = C

- Other toxicities**

If any grade  $\geq 3$  toxicity, withhold ibrutinib until resolved to grade 1 or baseline. Restart as per the dosing table above.

Toxicity	Definition	Dose adjustment
Haemorrhage	Unexpected bleeding	Discontinue
Bleeding risk pre and post-surgery	3 days prior to until 7 days post-op	Withhold Ibrutinib
Infection	Fever and constitutional upset	Withhold Ibrutinib

**Adverse effects** - for full details consult product literature/ reference texts

- Serious side effects**

Myelosuppression

Haemorrhage (subdural haematoma, GI bleeding, and haematuria)

Renal toxicity

Secondary primary malignancies

- Frequently occurring side effects**

Myelosuppression

Atrial fibrillation

Epistaxis

Abdominal pain

Pneumonia, upper respiratory tract infection

Diarrhoea

Nausea, vomiting

Rash

- Other side effects**

Fatigue

Musculoskeletal pain

Peripheral oedema  
Cough  
Dizziness  
Headache

### Significant drug interactions – for full details consult product literature/ reference texts

**Warfarin and other vitamin K antagonists** are contra-indicated during ibrutinib treatment.

**Strong or moderate CYP3A inhibitors** (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) - avoid concomitant use, and consider alternative agents. If strong CYP3A inhibitors cannot be avoided consider interrupting ibrutinib therapy for duration of inhibitor use (up to 7 days).

Avoid concomitant use of strong CYP3A inhibitors which need to be taken chronically (e.g. ritonavir, indinavir, nelfinavir, saquinavir).

If a moderate CYP3A inhibitor is used (e.g. fluconazole, erythromycin, diltiazem, atazanavir, imatinib, verapamil, ciprofloxacin), reduce the ibrutinib dose to 140mg for the duration of inhibitor use.

Patients taking concomitant strong or moderate CYP3A inhibitors should be monitored more closely for signs of ibrutinib toxicity.

**Seville oranges, grapefruit and grapefruit juice:** avoid as an inhibitor of CYP3A4 and may increase plasma concentrations of ibrutinib.

**Strong CYP3A inducers** (e.g. carbamazepine, rifampin, phenytoin and St. John's Wort) – avoid concomitant use, may decrease ibrutinib plasma concentration.

### Additional comments

Ibrutinib can cause foetal harm in pregnant women. Advise women to avoid becoming pregnant. Not known whether Ibrutinib is excreted in human milk.

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.

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### References

- Summary of Product Characteristics Ibrutinib (Janssen-Cilag), accessed 28 October 2015 via <http://www.medicines.org.uk>
- Byrd JC, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukaemia. *N Engl J Med* 2014; 371: 213-223.
- Wang M, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med* 2013; 369: 507-516.

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