**Ibrutinib**

**INDICATIONS**

Chronic lymphocytic leukaemia (CLL) or Small lymphocytic leukaemia (SLL) in adults who have a 17p deletion or TP53 mutation (**NICE TA429- BLUETEQ required**)

Relapsed or refractory CLL or SLL in adults (**NICE TA429- BLUETEQ required**) who

- Have had at least 1 prior anti-CD20- containing chemo-immunotherapy for CLL or SLL AND
- Are considered not appropriate for treatment or retreatment with purine analogue based therapy due to ONE of the following:
  - Failure to respond to chemo-immunotherapy.
  - A progression-free interval of less than 3 years.
  - Patients with a progression-free interval of less than 3 years with the preceding line of therapy
  - Progression-free interval of 3 years or more with the preceding line of therapy AND the presence of comorbidities that contraindicate consideration of chemoimmunotherapy.

NB- Starting from Sep 2018, patients with **progression-free interval of 3 years or more** and have **no** comorbidities can access ibrutinib via NHSE. Janssen will supply “red dot packs” for the first 3 months’ treatment, on confirmation of blueteq number.

Relapsed or refractory mantle cell lymphoma in adults who have had only 1 previous line of rituximab immunochemotherapy. (**NICE TA502- BLUETEQ required**) NB. Patients treated with 2-5 lines of prior therapy may still be eligible if Cancer Drug Fund criteria are met.

Relapsed Waldenstrom Macroglobulinaemia (WM) in adults who have received at least one prior therapy (**NICE TA491- BLUETEQ required**)

Newly diagnosed mantle cell lymphoma, with or without rituximab, instead of intravenous chemotherapy, in order to reduce toxicity of treatment and number of admissions required. **COVID Blueteq approval is required**

**TREATMENT INTENT**

Induction and maintenance of remission.
PRE-ASSESSMENT

1. Ensure histology is confirmed prior to administration of chemotherapy and document in notes.
2. Record stage of disease - CT scan (neck, chest, abdomen and pelvis), presence or absence of B symptoms, clinical extent of disease, consider bone marrow aspirate and trephine.
3. Blood tests - FBC, ESR, DAT, U&Es, LDH, urate, calcium, magnesium, creatinine, phosphate, LFTs, glucose, Igs, β2 microglobulin, hepatitis B core antibody and hepatitis BsAg, hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 after consent.
4. Urine pregnancy test - before cycle 1 of each new chemotherapy course in women of child-bearing age unless they are post-menopausal, have been sterilised or undergone a hysterectomy.
5. ECG +/- Echo and baseline BP in all patients with a cardiac history or at risk of cardiac complications (hypertension, smokers, diabetes)
6. Record performance status (WHO/ECOG).
7. Record height and weight.
8. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent prior to treatment.
9. Ensure pre-chemotherapy counselling in line with NPSA recommendation and chemotherapy measures.
10. Treatment should be agreed in the relevant MDT.

DRUG REGIMEN / CYCLE FREQUENCY

<table>
<thead>
<tr>
<th>CLL, SLL and WM</th>
<th>IBRUTINIB</th>
<th>420mg PO OD</th>
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</thead>
<tbody>
<tr>
<td>Mantle Cell Lymphoma</td>
<td>IBRUTINIB</td>
<td>560mg PO OD</td>
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</table>

Take at approximately the same time each day. Swallow the capsules whole with water. Do not open, break, or chew the capsules. Ibrutinib is available in both 90 and 120 pack sizes.

Avoid Seville oranges and grapefruit juice. See drug interaction section for use of concurrent CYP3A4 inhibitors.

RESTAGING

Clinical response should be assessed on a monthly basis for the first 3 months. It is important to realize that patients on Ibrutinib will develop worsening of lymphocytosis for the first 8-12 weeks and response cannot be assessed by a drop in lymphocytes.

Formal re-staging by CT at 3-6 months.
Subsequent CT scans should be considered every 3-6 months.
DOSE MODIFICATIONS

Interrupt Ibrutinib for any Grade 3 or greater non-haematological, Grade 3 or greater neutropenia with infection or fever, or Grade 4 haematological toxicities. Once symptoms of toxicity have resolved to Grade 1 or baseline (recovery), reintiate Ibrutinib at the starting dose. If the toxicity reoccurs, reduce dose by one capsule (140 mg). A second reduction of dose by 140 mg may be considered as needed. If toxicities persist or recur following two dose reductions, discontinue Ibrutinib.

<table>
<thead>
<tr>
<th>Toxicity Occurrence</th>
<th>Mantle Cell Lymphoma</th>
<th>CLL, SLL and WM</th>
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<tbody>
<tr>
<td>First</td>
<td>Restart at 560 mg daily</td>
<td>Restart at 420 mg daily</td>
</tr>
<tr>
<td>Second</td>
<td>Restart at 420 mg daily</td>
<td>Restart at 280 mg daily</td>
</tr>
<tr>
<td>Third</td>
<td>Restart at 280 mg daily</td>
<td>Restart at 140 mg daily</td>
</tr>
<tr>
<td>Fourth</td>
<td>Discontinue Ibrutinib</td>
<td>Discontinue Ibrutinib</td>
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</table>

Renal impairment  Recommendation  Hepatic impairment  Recommendation
[[CrCl < 30 mL/min or on dialysis][No data]  Child-Pugh Class A  280 mg daily
Child-Pugh Class B  140 mg daily
Child-Pugh Class C  No data

CONTRA-INDICATIONS

Platelet count < 35 x 10^9/L.
Concurrent use of warfarin.

INVESTIGATIONS

- FBC, creatinine monthly initially, extending to 3 monthly for stable patients.

Patients who are stable and without any side-effects could be monitored in a nurse-led clinic with blood pressure and pulse readings.

CONCURRENT MEDICATIONS

Co-trimoxazole  Consider PCP prophylaxis for all relapsed patients with a history of recurrent infections, and for patients on immunoglobulin replacement. **The clinician reviewing the requirement for PCP prophylaxis should document their decision on ARIA.**

480 mg daily on Mon/ Wed/ Fri for duration of treatment and for 3 months afterwards (Consider reducing the dose to 480 mg twice weekly during neutropenic periods).

This is a controlled document and therefore must not be changed or photocopied.
EMETIC RISK
Low.

DRUG INTERACTIONS
(Non this list is not conclusive. Always refer to the product SPC and consult with a pharmacist.)
Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A4.

CYP3A4 inhibitors
Avoid concomitant administration of IMBRUVICA with strong or moderate inhibitors of CYP3A4. For strong CYP3A4 inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, consider interrupting Ibrutinib therapy during duration of inhibitor use or reduce dose to 140mg daily. If a moderate CYP3A inhibitor must be used, reduce the Ibrutinib dose to 280mg daily. Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored closely for signs of Ibrutinib toxicity. Avoid Seville oranges and grapefruit, as these contain moderate CYP3A inhibitors.

CYP3A4 inducers
Administration of Ibrutinib with strong inducers of CYP3A decreases Ibrutinib plasma concentrations by approx 10-fold. Avoid concomitant use of strong CYP3A inducers e.g., carbamazepine, rifampin, phenytoin and St. John’s Wort. Consider alternative agents with less CYP3A4 induction.

WARNINGS AND SPECIAL PRECAUTIONS

Haemorrhage: 5% at Grade 3 or higher bleeding events (subdural hematoma, GI bleeding, haematuria). Overall, 48% at any grade at full dose. Consider benefit-risk with concurrent antiplatelet or anticoagulant therapies, and of withholding Ibrutinib for at least 3 to 7 days pre and post-surgery depending on type of surgery and risk of bleeding.

Infections: Fatal and non-fatal. At least 25% at Grade 3 or greater. Monitor fever and infections and evaluate promptly.

Cardiac complications: Ventricular tachyarrhythmia and sudden cardiac death

Myelosuppression: 41% at Grade 3 or 4 (neutropenia (29%), thrombocytopenia (17%), anaemia (9%)). Monitor FBC monthly.

Renal toxicity: Fatal and serious cases - increases in creatinine levels up to 1.5 x ULN in 67%, 1.5 - 3 x ULN in 9%. Periodically monitor creatinine levels. Maintain hydration.

Second primary malignancies: 5% occurrence in patients - skin cancers (4%), and other (1%).

Hepatitis B reactivation: establish hepatitis B virus status before initiating ibritinib and consult a liver disease expert for monitor and management in patients with positive hepatitis B serology.
ADVERSE REACTIONS
(Consult with pharmacist and refer to SPC for full details)

≥ 20%: thrombocytopenia, diarrhoea, neutropenia, anaemia, fatigue, musculoskeletal pain, peripheral oedema, upper respiratory tract infection, nausea, bruising, dyspnoea, constipation, rash, abdominal pain, vomiting, decreased appetite, Grade 3 or 4 non-haematological adverse reactions (≥ 5%): pneumonia, abdominal pain, atrial fibrillation, diarrhoea, fatigue, skin infections.

Others: stomatitis, dyspepsia, urinary tract infection, sinusitis, peripheral oedema, asthenia, petechiae, muscle spasms, arthralgia, cough, epistaxis, dehydration, dizziness, headache.

TREATMENT RELATED MORTALITY

Less than 5 %

REFERENCES

2. MHRA. Ibrutinib (Imbruvica): reports of ventricular tachyarrhythmia; risk of hepatitis B reactivation and of opportunistic infections. Published 15/08/2017. [Link]

Review

<table>
<thead>
<tr>
<th>Name</th>
<th>Revision</th>
<th>Date</th>
<th>Version</th>
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<tbody>
<tr>
<td>Cheuk-kie Cheung (Pharmacist)</td>
<td>Updated NHSE commissioning for CLL, PCP prophylaxis review and general formatting</td>
<td>Sep 2018</td>
<td>2.1</td>
<td>May 2020</td>
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<tr>
<td>Faouzi Djebbari</td>
<td>Update with the new indication during COVID-19 pandemic</td>
<td>June 2020</td>
<td>2.2</td>
<td>May 2021</td>
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</table>
L.38 Ibrutinib
Authorised by CLL lead
Dr Anna Schuh
Authorised by Lymphoma lead
Dr Graham Collins
Date: May 2018

Published: May 2014
Reviewed: May 2018
Updated: June 2020
Review: May 2021

Version 2.2