**DRUG ADMINISTRATION SCHEDULE**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Cycle Length</th>
<th>Drug</th>
<th>Daily Dose</th>
<th>Route</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Lymphocytic Leukaemia</td>
<td>Continuous</td>
<td>Ibrutinib</td>
<td>420mg (three capsules)</td>
<td>Oral</td>
<td>ONCE daily</td>
</tr>
<tr>
<td>Mantel Cell Lymphoma</td>
<td>Continuous</td>
<td>Ibrutinib</td>
<td>560mg (four capsules)</td>
<td>Oral</td>
<td>ONCE daily</td>
</tr>
</tbody>
</table>

- Ibrutinib is presented as 140mg hard capsules these should be swallowed whole with a glass of water at approximately the same time each day
- Grapefruit, grapefruit juice and Seville oranges should be avoided whilst on ibrutinib.

**CYCLE LENGTH AND NUMBER OF DAYS**

Ibrutinib treatment is continuous as long as clinical benefit is observed or until unacceptable toxicity occurs.

**APPROVED INDICATIONS:**

The treatment of relapsed/ refractory Chronic Lymphocytic Leukaemia where all the following criteria are met:

1. Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
2. Confirmed CLL
3. Must have received at least one prior anti-CD20 - containing chemo-immunotherapy for CLL
4. Considered not appropriate for treatment or retreatment with purine analogue based therapy due to:
   a. Failure to respond to chemo-immunotherapy OR
   b. A progression-free interval of less than 3 years OR
   c. Age of 70yrs or more OR
   d. Age of 65yrs or more plus the presence of comorbidities OR
   e. A 17p or TP53 deletion 5.
5. A performance status of ECOG 0-2 6
6. A neutrophil count of ≥0.75 x 10⁹/l
7. A platelet count of ≥30 x 10⁹/l
8. Patient not on warfarin or CYP3A4/5 inhibitors
9. No prior treatment with idelalisib unless idelalisib has 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.
The treatment of relapsed/ refractory Mantle Cell Lymphoma where all the following criteria are met:

1. Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
2. Confirmed Mantle Cell Lymphoma with cyclin D1 overexpression or translocation breakpoints at t(11;14)
3. Failure to achieve at least partial response (PR) with, or documented disease progression disease after, the most recent treatment regimen
4. An ECOG performance status of PS 0-2
5. At least one but no more than five previous lines of treatment

Note: Patients receiving Ibrutinib via the compassionate use programme should not be switched to CDF funding. Free of charge supplies from the manufacturer should continue to be used in these patients until NICE approval and as per the terms of the compassionate use programme

PREMEDICATION
None required as standard

RECOMMENDED TAKE HOME MEDICATION
None required as standard

INVESTIGATIONS / MONITORING REQUIRED
Pre-treatment blood test(s): FBC, U/E, LFTs, Coagulation screen, Immunoglobulins
Labs prior to each cycle: FBC, U/E, LFTs
Scans: As appropriate to disease type and stage to allow assessment of response

ASSESSMENT OF RESPONSE
CLL: Peripheral full blood count, lymphocyte count, Palpable lymph node and spleen size. Lymphadenopathy by scan as appropriate. Bone marrow assessment

REVIEW BY CLINICIAN
To be reviewed by either a Nurse, Pharmacist or Clinician before every cycle.

NURSE / PHARMACIST LED REVIEW
Each cycle as applicable according to local protocols
ADMINISTRATION NOTES

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A4; therefore inhibitors of CYP3A4 may reduce the metabolism of ibrutinib and increase its plasma concentration. Patients requiring CYP3A4 inhibitors concurrently with ibrutinib should be monitored closely for toxicity and follow the dose modification guidance as below.

CYP3A4 inhibitors

Strong inhibitors of CYP3A4 (e.g. ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin,itraconazole, nefazodon and cobicistat) should be avoided and to a lesser extent moderate CYP3A4 inhibitors (e.g. voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, dronedarone). If the benefit outweighs the risk and a CYP3A4 inhibitor must be used, reduce the ibrutinib dose to 140 mg (one capsule). Alternatively if a strong CYP3A4 inhibitor is being used ibrutinib treatment can be temporarily withheld (for 7 days or less) instead of dose reducing ibrutinib.

Agents that may decrease ibrutinib plasma concentrations

Avoid concomitant use of strong or moderate CYP3A4 inducers (e.g. carbamazepine, rifampicin, phenytoin). Preparations containing St. John's Wort are contraindicated during treatment with Ibrutinib, as efficacy may be reduced.

Agents that may have their plasma concentrations altered by ibrutinib

Narrow therapeutic range P-gp substrates such as digoxin should be taken at least 6 hours before or after Ibrutinib.

Women of child-bearing potential/Contraception in females

Ibrutinib may cause foetal harm. Therefore women of child-bearing potential must use highly effective contraceptive measures while taking Ibrutinib and for three months after stopping treatment. Women using hormonal contraceptives should add a barrier method as it is currently unknown whether ibrutinib reduces the effectiveness of hormonal contraceptives.

Bleeding-related events

Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib due to the risk of haemorrhagic events. Patients requiring anti-platelet medication or other anti-coagulants also have an increased risk of bleeding whilst on ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided.

Surgery

Ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.
IBRUTINIB (IMBRUVICA ®) for Chronic Lymphocytic Leukaemia and Mantel Cell Lymphoma

Cumbria, Northumberland, Tyne & Wear Area Team

TOXICITIES

Neutropenia, anaemia, diarrhoea, musculoskeletal pain, upper respiratory tract infection, bruising, rash, nausea, pyrexia, pneumonia and thrombocytopenia.

DOSE MODIFICATION / TREATMENT DELAYS

Haematological Toxicity:

Dose delay if neutrophils < 1.0x 10^9/L with infection or fever or neutrophils < 0.5x 10^9/L or platelets <30 x 10^9/L. Restart once the toxicity has resolved to grade 1 using the dosing table shown below.

<table>
<thead>
<tr>
<th>Toxicity occurrence</th>
<th>MCL dose modification after recovery</th>
<th>CLL dose modification after recovery</th>
</tr>
</thead>
<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>
</tr>
</tbody>
</table>

Non- Haematological Toxicity:

Dose delay for any new onset or worsening grade non-haematological toxicity as below. Restart once the toxicity has resolved to grade 1 using the dosing table above.

<table>
<thead>
<tr>
<th>Non-haematological grade</th>
<th>Ibrutinib dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>No change</td>
</tr>
<tr>
<td>2</td>
<td>No change</td>
</tr>
<tr>
<td>≥ 3</td>
<td>Withhold, restart once the toxicity has resolved to grade 1 using the dosing table shown above</td>
</tr>
</tbody>
</table>

Renal Impairment

<table>
<thead>
<tr>
<th>Stage of renal impairment</th>
<th>Ibrutinib dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>mild or moderate renal impairment (greater than 30 mL/min creatinine clearance)</td>
<td>No change</td>
</tr>
<tr>
<td>severe renal impairment (&lt; 30 mL/min creatinine clearance)</td>
<td>Administer Ibrutinib only if the benefit outweighs the risk and monitor closely for signs of toxicity</td>
</tr>
<tr>
<td>patients on dialysis</td>
<td>No data available</td>
</tr>
</tbody>
</table>

Hepatic Impairment

Ibrutinib is metabolised in the liver. Monitor patients for signs of ibrutinib toxicity and follow dose modification guidance below as needed.
**Liver Impairment** | **Ibrutinib Dose**
--- | ---
Child-Pugh class A | 280 mg daily (two capsules)
Child-Pugh class B | 140 mg daily (one capsule)
Child-Pugh class C | Not recommended

**TREATMENT LOCATION**
Can be given at Cancer Centre or Cancer Unit

**REFERENCES:**
2. Wang et al; Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma; 2013; 369:507-16

**Document Control**

<table>
<thead>
<tr>
<th>Document Title:</th>
<th>Ibrutinib for CLL and MCL CRP15-H045</th>
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<tr>
<td>Document No:</td>
<td></td>
</tr>
<tr>
<td>Current Version:</td>
<td>1.1</td>
</tr>
<tr>
<td>AuthorS:</td>
<td>Lynne Thompson/Jonathan Wallis/Tobias Menne</td>
</tr>
<tr>
<td>Approved by:</td>
<td>Chemotherapy Group</td>
</tr>
<tr>
<td>Due for Review:</td>
<td>23.11.17</td>
</tr>
<tr>
<td>Date Approved:</td>
<td>23.11.15</td>
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<tr>
<td>Summary of Changes</td>
<td>1.1 Updated CDF approval criteria</td>
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