Ibrutinib (Imbruvica) for relapsed and refractory marginal zone lymphoma – second or subsequent line

LAY SUMMARY

Marginal zone lymphoma is a type of cancer which usually develops very slowly. In people with marginal zone lymphoma, the body makes too many white blood cells called B-lymphocytes. These lymphocytes are abnormal and do not work properly and build up in different parts of the body such as the gut, salivary glands, eyes, spleen, and lymph nodes.

Ibrutinib is a new type of drug for patients with marginal zone lymphoma given as a tablet once a day. Some studies have suggested ibrutinib may be helpful for people whose first treatment has failed and whose disease has spread.

If ibrutinib is licensed for use in the UK, it could be a new treatment option for patients with marginal zone lymphoma that may reduce symptoms of the disease and increase survival.

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This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.
TARGET GROUP

- Marginal zone lymphoma (MZL): relapsed and refractory – second or subsequent line.

TECHNOLOGY

DESCRIPTION

Ibrutinib (Imbruvica; JNJ54179060; PCI 32765) is a selective Bruton’s tyrosine kinase (Btk) inhibitor. It acts by blocking B-cell antigen receptor signalling, thereby arresting the cell cycle and inducing cell death. As Btk is not found in T-cells, ibrutinib does not affect T-cell receptor signalling. In a phase III clinical trial, ibrutinib was administered orally, at 560mg (4 x 140mg capsules) once daily1.

Ibrutinib is licensed in the EU for the treatment of adult patients with:
- Mantle cell lymphoma; second line.
- Chronic lymphocytic leukaemia; first or second line.
- Waldenström's macroglobulinaemia; first or second line.

Very common (≥10%) reported adverse events include pneumonia, upper respiratory tract, skin and urinary tract infections, sinusitis, neutropenia, thrombocytopenia, anaemia, dizziness, headache, haemorrhage, epistaxis, bruising, petechiae, diarrhoea, vomiting, constipation, rash, arthralgia, musculoskeletal pain, pyrexia and peripheral oedema2.

Ibrutinib is also in phase III development for non-Hodgkin's lymphoma, diffuse large B cell lymphoma, and pancreatic cancer. It is in phase II development for hairy cell leukaemia, follicular lymphoma and acute myeloid leukaemia.

INNOVATION and/or ADVANTAGES

If licensed, ibrutinib will offer an additional oral treatment option for patients with relapsed and refractory MZL.

DEVELOPER

Janssen-Cilag UK.

AVAILABILITY, LAUNCH OR MARKETING

Ibrutinib is a designated orphan drug in the USA and currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Lymphoma is a cancer of the lymphatic system resulting in malignant lymphoid neoplasms of B or T-cell origin3. There are two main types of lymphoma: Hodgkin lymphoma and non-Hodgkin lymphoma (NHL). Approximately 80% of all lymphomas diagnosed are NHL4. MZL is a type of B-cell NHL3 recognised by the World Health Organization as 3 entities: nodal MZL, splenic MZL, and extranodal MZL of mucosa-associated lymphoid tissue (MALT)5.
These subtypes display different characteristics, with variations in clinical presentation and prognosis according to the organ where the lymphoma arises.

MALT is the most common type of MZL, affecting lymphoid tissue found in the gut, salivary glands, thyroid gland, eyes, and lungs. MALT lymphomas usually start in areas of the body where there has been long-term inflammation due to an infection or autoimmune condition. It makes up approximately 9-10% of all NHL. Symptoms of MALT include indigestion, stomach pain, nausea, and anaemia. Nodal MZL is a rare form of NHL, which affects lymphocytes at the margins of lymph nodes. It makes up approximately 2% of all cases of NHL. Symptoms of nodal MZL include enlarged lymph nodes of the neck, armpit, groin or stomach, and frequent, persistent infections. Splenic MZL is the rarest subtype of MZL, and affects lymphocytes in the spleen. It makes up approximately 1% of all cases of NHL. Symptoms of splenic MZL include enlargement of the spleen, abdominal pain, and abnormal blood count. Nodal MZL has been reported to confer a worse prognosis, whereas splenic MZL is considered to be the most indolent subtype.

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:

**CLINICAL NEED and BURDEN OF DISEASE**

NHL is the sixth most common cancer in the UK; in 2013, there were 11,392 new cases of NHL diagnosed in England. It is estimated that MZL accounts for 20% of all NHL cases. Approximately 71% of people diagnosed with MZL are over the age of 65, with a median age at diagnosis of 72 years. Around 78% of these patients have stage III or IV disease at diagnosis. It is estimated that the annual incidence of MZL in the UK is 3.5 per 100,000 population. The estimated 10-year prevalence of MZL in the UK is 13,638 or 23 per 100,000 population.

Overall, more than 60% of people with NHL will live at least 10 years. In 2013, in the UK there were approximately 2,596 deaths from NHL (ICD-10 C85). Five-year survival estimates vary between MZL sub-types: systemic (nodal and splenic) MZL 5-year overall and relative survival rates are 75% and 89% respectively, compared with 57% and 81% for MALT MZL. The 5-year overall survival rate for all MZL sub-types is 61%. In 2013-14, there were 20,968 admissions for NHL (ICD-10 C85) in England, resulting in a total of 33,673 bed days and 22,655 finished consultant episodes.

The population likely to be eligible to receive ibrutinib could not be estimated from available published sources.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**
• NICE technology appraisal in development. Lymphoma (non-Hodgkin’s) – bendamustine (with rituximab) [ID434]. Anticipated publication date to be confirmed.
• NICE technology appraisal. Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin’s lymphoma (TA137). February 2008.

Other Guidance

• European Society for Medical Oncology. Gastric Marginal Zone Lymphoma of MALT Type: ESMO Clinical Practice Guidelines. 201320.

CURRENT TREATMENT OPTIONS

The indolent nature of MZL justifies a conservative approach to treatment, particularly when patients are diagnosed with stage I or II disease. Expert opinion suggests that a high proportion of patients, approximately 50%, are initially actively monitored and do not receive treatmenta. Some patients will never require therapy but others will progress with time and eventually need treatmenta. Approximately 47% of patients18 with MALT MZL are diagnosed at stage I and receive fairly minimal therapy or antibiotic prophylaxis onlya.

Treatment options may differ according to MZL subtype, and may include7,21,22,23:

• Splenic MZL
  o Active monitoring and observation.
  o Splenectomy.
  o Single agent chemotherapy: chlorambucil, cyclophosphamide, fludarabine, cladribine.
  o Combination chemotherapy: FCR (fludarabine, cyclophosphamide and rituximab)
  o Immunotherapy: rituximab (alone or together with chemotherapy), R-FMD (rituximab, fludarabine, mitoxantrone and dexamethasone).
  o Radiotherapy.

• Nodal MZL
  o Active monitoring and observation.
  o Single agent chemotherapy: chlorambucil, fludarabine, cladribine.
  o Combination chemotherapy: CVP (cyclophosphamide, vincristine and the steroid prednisolone), CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone).
  o Immunotherapy: rituximab (alone or together with chemotherapy)
  o Antiviral agents.
  o Radiotherapy.
  o Stem cell transplantation.

• MALT MZL
  o Active monitoring and observation.
  o Surgery.
  o Chemotherapy: chlorambucil, cyclophosphamide, bendamustine.
  o Immunotherapy: rituximab

a Expert personal communication.
- Helicobacter pylori-positive gastric MALT eradication therapy.
- Radiotherapy.

**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01980628, PCYC-1121-CA; ibrutinib; phase II.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Janssen Research and Development.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry¹.</td>
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<tr>
<td>Location</td>
<td>EU (incl UK) and USA.</td>
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<tr>
<td>Design</td>
<td>Non-randomised, uncontrolled.</td>
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<tr>
<td>Participants</td>
<td>n=60 (planned); aged ≥18 years; marginal zone lymphoma including splenic, nodal, and extranodal sub-types; progression despite one or more lines of therapy including at least one CD20-directed regimen; no CNS lymphoma or leptomeningeal disease.</td>
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<tr>
<td>Schedule</td>
<td>Ibrutinib orally at 560mg once daily.</td>
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<td>Follow-up</td>
<td>Active treatment for 1 year, follow-up 5 years.</td>
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<td>Primary outcome</td>
<td>Overall response rate.</td>
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<td>Secondary outcomes</td>
<td>Frequency, severity, and relatedness of adverse events, duration of response, pharmacokinetics, progression-free survival, and overall survival.</td>
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<tr>
<td>Expected reporting date</td>
<td>Study primary completion date reported as Sept 2015.</td>
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**ESTIMATED COST and IMPACT**

**COST**

Ibrutinib (Imbruvica) is already marketed in the UK; a pack of 90 x 140mg tablets costs £4,599.00.

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Other: expert opinion suggests that the majority of patients who relapse following first line therapy are elderly, who may find current second line treatment options difficult to tolerate². If ibrutinib is an effective and relatively non-toxic therapy, this could improve both quality of life and survival in this patient group³.
- Reduced symptoms or disability
- No impact identified

**Impact on Health and Social Care Services**

- Increased use of existing services
- Decreased use of existing services: the company states that ibrutinib is expected to

² Expert personal communication.
reduce inpatient admissions for treatment of complications and for use of supportive care drugs.

- Re-organisation of existing services
- Other
- Need for new services
- None identified

### Impact on Costs and Other Resource Use

- Increased drug treatment costs
- Other increase in costs.
- Other: the company states that costing information cannot be accurately calculated as duration of therapy is not yet known.
- Reduced drug treatment costs
- Other reduction in costs.
- None identified

### Other Issues

- Clinical uncertainty or other research question identified.
- None identified

### REFERENCES

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professional/cancer-statistics/statistics-by-cancer-type/non-hodgkin-lymphoma#heading-Two
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September.
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