Ixazomib in combination with oral dexamethasone for relapsed or refractory systemic light chain (AL) amyloidosis

SUMMARY

Ixazomib in combination with oral dexamethasone is intended to be used as a second line therapy for the treatment of relapsed or refractory systemic light chain amyloidosis in patients who have previously received one or two other therapies. If licensed, ixazomib will offer an additional treatment option for this patient group.

Systemic light chain (AL) amyloidosis (formerly known as primary amyloidosis) is the most common of the three types of systemic amyloidosis (the others being AA and ATTR). The incidence of AL amyloidosis in England was estimated to be 0.5 per 100,000 population in 2008. Those diagnosed with a form of amyloidosis are estimated to have a median survival of 45 months. 306 deaths from all types of amyloidosis were registered in England and Wales during 2012. The proportion of patients with relapsed or refractory AL amyloidosis is not known, therefore the numbers eligible to receive ixazomib could not be estimated from available routine published sources.

Chemotherapy is the main treatment for AL amyloidosis and there are a number of regimens available depending on patient frailty and previous treatment. Such treatment is directed at the underlying bone marrow disorder with the aim of decreasing the abnormal amyloid producing plasma cells, which in turn may inhibit disease progression and induce regression of existing amyloid deposits. Ixazomib in combination with oral dexamethasone for AL amyloidosis is currently in a phase III clinical trial comparing its effect on haematologic response, 2-year vital organ deterioration and mortality against clinicians choice of treatment in combination with dexamethasone. This trial is expected to complete in early 2016.
TARGET GROUP

- Systemic light chain (AL) amyloidosis: relapsed or refractory after 1 or 2 prior therapies - second line; in combination with oral dexamethasone.

TECHNOLOGY

DESCRIPTION

Ixazomib (MLN9708) is a small molecule, second generation proteasome inhibitor. Proteasome inhibitors act on cancer cells by inducing apoptosis via the disruption of essential protein synthesis in the highly proliferative tumour cells. In the phase III clinical trials, ixazomib is administered orally at 4mg on days 1, 8, and 15 of a 28 day cycle in combination with oral dexamethasone at 20 mg on days 1, 8, 15, and 22 of each 28 day cycle. Treatment was continued until disease progression or unacceptable toxicity.

Ixazomib does not currently have Marketing Authorisation in the EU for any indication.

Ixazomib is also in phase III clinical trials for relapsed and/or refractory multiple myeloma and first line multiple myeloma and in phase II trials for follicular lymphoma.

INNOVATION and/or ADVANTAGES

If licensed, ixazomib will offer an additional treatment option for people with relapsed or refractory systemic light chain (AL) amyloidosis.

DEVELOPER

Takeda Pharmaceuticals Ltd.

AVAILABILITY, LAUNCH OR MARKETING

Ixazomib is a designated orphan drug in the EU and USA. It is currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Amyloidosis is a group of plasma cell disorders characterised by the abnormal folding, aggregation and accumulation of certain proteins in the body’s tissues in an abnormal form known as amyloid deposits. These deposits can interfere with organ function, particularly when the disease is systemic i.e. found throughout the body. Systemic light chain (AL) amyloidosis (formerly known as primary amyloidosis) is the most common of the three types of systemic amyloidosis (the others being AA and ATTR). In AL amyloidosis a small clonal plasma cell population in the bone marrow produce excess amyloidogenic monoclonal immunoglobulin light chains which form the amyloid deposits. In most patients, AL amyloidosis is caused by an underlying bone marrow disorder, where the abnormal plasma cells are produced. In around 20% of patients with the disease, these cells replicate more aggressively and have the potential to become overtly cancerous leading to myeloma.
AL amyloidosis may be found secondary to multiple myeloma in 10-15% of patients, but rarely does AL amyloidosis progress to multiple myeloma.\(^2\)\(^3\).

Symptoms of AL amyloidosis depend upon the organs affected; it can therefore be difficult to diagnose. Symptoms may include fatigue, weight loss, oedema, shortness of breath, and light-headedness.\(^4\) The severity and impact of the disease on individual patients also depends on the organs affected. The most common clinical features include: nephritic syndrome with or without renal insufficiency, congestive cardiomyopathy, sensorimotor and/or automatic peripheral neuropathy and hepatomegaly.\(^5\) In particular, where organs such as the heart, kidneys, liver, digestive system or nerves are involved, a patient may experience a severe impact on their health and quality of life.\(^2\)

### NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:

### CLINICAL NEED and BURDEN OF DISEASE

In 2008, the incidence of amyloidosis in England was estimated to be 0.8 per 100,000, based on cases seen at the National Amyloidosis Centre, an estimate of undiagnosed cases and an estimate of those treated elsewhere.\(^6\) AL amyloidosis was thought to make up a significant proportion of these cases at 0.5 per 100,000 population.\(^6\) AL amyloidosis is more common in men than women and the majority of patients are over 45 years old, though it can sometimes occur in younger age groups.\(^7\) Those diagnosed with amyloidosis are estimated to have a median survival of 45 months (95% CI 43.2-46.7).\(^6\)

In 2012-13, there were 1,707 admissions for all types of amyloidosis (ICD-10 E85) in England, resulting in 2,034 bed-days and 2,034 finished consultant episodes.\(^8\) More specifically, in 2012-13 there were 185 admissions for other amyloidosis (ICD-10 E85.8) in England, which includes AL amyloidosis amongst other types of the disease, resulting in 399 bed-days and 203 finished consultant episodes.\(^8\) 517 admissions were recorded for unspecified amyloidosis (ICD-10 E85.9), resulting in 1,357 bed days and 585 finished consultant episodes.\(^8\) 306 deaths from all types of amyloidosis were registered in England and Wales during 2012.\(^9\) Of these, 4 deaths were from other amyloidosis and 96 deaths were recorded as amyloidosis unspecified.\(^9\) The proportion of patients with relapsed or refractory AL amyloidosis is not known, therefore the numbers eligible to receive ixazomib could not be estimated from available routine published sources.

### PATIENT PATHWAY

### RELEVANT GUIDANCE

**NICE Guidance**

None Identified.
OTHER GUIDANCE

- Guidelines Working Group of the UK Myeloma Forum on behalf of the British Committee for Standards in Haematology (BCSH), Guidelines on the diagnosis and management of AL amyloidosis. 2004\(^11\),\(^a\).

CURRENT TREATMENT OPTIONS

Treatment for AL amyloidosis is directed at the underlying bone marrow disorder with the aim of decreasing the abnormal amyloid producing plasma cells, which in turn may inhibit disease progression and induce regression of existing amyloid deposits\(^12\). Treatment for AL amyloidosis is predominately chemotherapy based, but is often combined with symptomatic therapies to support the function of affected organs and general patient wellbeing\(^12\).

Primary chemotherapy treatment options include\(^5,12\):

**High Dose**
- High dose intravenous (IV) melphalan (unlicensed for this indication) with stem-cell transplant\(^5,12\).

**Intermediate Dose**
- Cyclophosphamide, thalidomide (unlicensed for this indication) and dexamethasone (CTD) protocol\(^5,12\).
- Cyclophosphamide, bortezomib (unlicensed for this indication) and dexamethasone (CVD) protocol\(^5,12\).
- Melphalan (unlicensed for this indication) and dexamethasone\(^5,12\).
- Bortezomib and dexamethasone\(^5,12\).
- Bortezomib, melphalan and prednisolone\(^12\).
- Dexamethasone and alpha-interferon\(^5\) (unlicensed for this indication).
- Dexamethasone and thalidomide\(^5\).
- Dexamethasone and lenalidomide\(^5\) (unlicensed for this indication).
- Dexamethasone, cyclophosphamide and lenalidomide\(^5\).
- Dexamethasone and pomalidomide\(^5\) (unlicensed for this indication).

**Low Dose**
- Melphalan and prednisolone\(^12\).

In general, patients with relapsed and/or refractory disease will be treated with an alternative drug combination to that they have already received\(^13\). For instance, lenalidomide and dexamethasone, pomalidomide and dexamethasone, cyclophosphamide/melphalan with lenalidomide and dexamethasone, bendamustine or bortezomib are potential treatments for this group\(^14\). However, no consensus exists on the most appropriate approach or their sequential treatment order\(^14\).

\(^a\) The British committee for standards in haematology are currently updating their AL amyloidosis guidelines
### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>TOURMALINE AL-1, NCT01659658, C16011, 2011-005468-10, EUCTR2011-005468-10-DE, MLN9708; ixazomib plus dexamethasone vs one of melphalan, cyclophosphamide, thalidomide or lenalidomide, all in combination with dexamethasone, or dexamethasone alone.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Millennium Pharmaceuticals, Inc.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial Registry 1b</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada, Australia, Israel, and Republic of Korea.</td>
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<tr>
<td>Design</td>
<td>Randomised, active-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=248 (planned); aged ≥18 years; AL amyloidosis; relapsed or refractory after 1 or 2 prior therapies, patients may be proteasome inhibitor-exposed or naïve but not refractory to proteasome inhibitor therapy.</td>
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</tbody>
</table>
| Schedule             | Randomised to ixazomib, 4mg orally on days 1, 8, and 15 of each 28 day cycle, plus dexamethasone, 20mg orally on days 1, 8, 15 and 22 of each 28 day cycle; or physician’s choice of one of the following:  
  - Dexamethasone, 20mg orally on days 1-4, 9-12 and 17-20 of each 28 day cycle.  
  - Dexamethasone, 20mg orally on days 1-4 of each 28 day cycle plus melphalan, 0.22mg/kg orally on days 1-4 every 28 days.  
  - Dexamethasone, 20mg orally on days 1, 8, 15 and 22 of each 28 day cycle plus cyclophosphamide, 500mg orally on days 1, 8 and 15 of each 28 days.  
  - Dexamethasone, 20mg orally on days 1, 8, 15 and 22 of each 28 day cycle plus daily thalidomide, total dose up to 200mg orally.  
  - Dexamethasone, 20mg orally on days 1, 8, 15 and 22 of each 28 day cycle plus lenalidomide, 15mg orally for days 1-21 of each 28 day cycle.  
  In all treatment arms dexamethasone may be increased to 40mg after 4 weeks if lower dose is tolerated without any grade 2+ dexamethasone-related toxicities. |
| Follow-up            | Active treatment until disease progression or unacceptable toxicity. Follow-up 2 years or until death.                                                                                               |
| Primary outcome/s    | Overall haematologic response; 2-year vital organ deterioration; mortality rate.                                                                                                                  |
| Secondary outcome/s  | Complete haematologic response; overall survival; progression-free survival; haematologic disease progression-free survival; time to vital organ deterioration; number of patients with cardiac and/or kidney response; vital organ progression-free survival; duration of haematologic response; adverse events (AEs); time to treatment failure; time to subsequent anticancer treatment; quality of life (EQ-5D scores); number of medical encounters. |
| Expected reporting date | Study completion date reported as early 2016.                                                                                                  |

### ESTIMATED COST and IMPACT

#### COST

The cost of ixazomib is not yet known.

The costs of other selected treatments for AL amyloidosis are summarised as follows:
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Cost £️ per cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>20mg, oral, on days 1, 8, 15 and 22 every 28 days</td>
<td>£5.64</td>
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<tr>
<td>Melphalan</td>
<td>17mg*, oral, on days 1-4 every 28 days</td>
<td>£61.75</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>500mg, oral, on days 1,8, and 15 every 28 days</td>
<td>£21.21</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Up to a 200mg, oral, total dose per day</td>
<td>Up to £1193.92</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>15mg, oral, on days 1-21 of a 28 day cycle</td>
<td>£3969</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1.88mg**, IV, on days 1,4,8 and 11 every 21 days</td>
<td>£2287.14</td>
</tr>
</tbody>
</table>

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**
- ☑ Reduced mortality/increased length of survival
- ☑ Reduced symptoms or disability
- ☐ Other:
- ☐ No impact identified

**Impact on Health and Social Care Services**
- ☑ Increased use of existing services
- ☐ Decreased use of existing services
- ☐ Re-organisation of existing services
- ☐ Need for new services
- ☐ Other:
- ☐ None identified

**Impact on Costs and Other Resource Use**
- ☐ Increased drug treatment costs
- ☑ Reduced drug treatment costs
- ☐ Other increase in costs:
- ☐ Other reduction in costs:
- ☑ Other: uncertain unit cost compared to existing treatments
- ☐ None identified

**Other Issues**
- ☑ Clinical uncertainty or other research question identified: *Ixazomib’s role in AL amyloidosis is dependent on the rapidity, depth and duration of the clonal response achieved and how well tolerated treatment is. If it improves clonal responses it could be useful in patients with treatment refractory or relapsed disease*.

*However, assessing patient outcomes in AL amyloidosis is difficult. Assessment by clonal response can indicate treatment efficacy, survival and changes in organ function, but the pleomorphic nature of the disease means that some patients with specific organ involvement will not improve even with a significant clonal response. Amyloid regression and organ improvement also depends on how efficiently an individual patient can clear amyloid deposits and the potential of the affected organs to recover*.

- ☐ None identified

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*Based on average adult bodyweight of 77.9kg
*Based on the average adult body surface area of 1.88m²
*Expert personal opinion
*Expert personal opinion
REFERENCES