Plitidepsin (Aplidin) for relapsed and refractory multiple myeloma – fourth line

LAY SUMMARY

Multiple myeloma is a cancer which develops in the bone marrow from plasma cells (a type of white blood cell). Multiple myeloma is more common in men than women and also more common in older people.

For most patients, multiple myeloma is not curable. Treatment is often successful at first but then it begins to stop working and the disease returns.

Plitidepsin is a new drug being developed for the treatment of multiple myeloma that is delivered straight into the blood stream via a drip every two weeks.

Some studies have suggested that plitidepsin may be helpful for people whose first three treatments have already failed and whose disease has spread. More studies are now aiming to show how well it works and whether it is safe to use.

NIHR HSRIC ID: 10668
TARGET GROUP

- Multiple myeloma: relapsed and refractory – fourth line in patients who have received bortezomib and lenalidomide-containing regimens (or thalidomide where lenalidomide is not available, unless unable to tolerate either drug); in combination with dexamethasone.

TECHNOLOGY

DESCRIPTION

Plitidepsin (Aplidin, dehydrodidemnin B) is a cyclic depsipeptide identified from the Mediterranean marine tunicate, *Aplidium albicans*. It induces rapid and persistent activation of apoptosis in tumour cells by induction of early c-Jun N-terminal kinases (JNK) and p38 MAPK, leading eventually to mitochondrial cytochrome C release that initiates the apoptosis cascade by means of caspase cascade activation. It also inhibits Vascular Endothelial Growth Factor (VEGF) secretion and down-regulates VEGF receptor-1 in leukaemia cell lines (MOLT-4), blocking an essential loop for cell proliferation; inhibits elongation factor 1-α, interfering with protein synthesis; and induces G1 arrest and G2 blockade. In the phase III clinical trial, plitidepsin is administered by intravenous (IV) infusion at 5mg/m² IV on day 1 and 15 of a 28-day cycle in combination with dexamethasone 40mg orally on days 1, 8, 15 and 22 of a 28-day cycle¹.

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

INNOVATION and/or ADVANTAGES

If licensed, plitidepsin in combination with dexamethasone will offer an additional treatment option for patients with relapsed or refractory multiple myeloma who have received standard bortezomib and lenalidomide-containing regimens. Patients who experience relapse after treatment with the immunomodulatory agent lenalidomide and proteasome inhibitor bortezomib have a particularly poor prognosis², with median overall survival of nine months³.

DEVELOPER

Pharma Mar S.A.; Chugai Pharmaceutical Co. Ltd (UK licensee).

AVAILABILITY, LAUNCH OR MARKETING

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

PATIENT GROUP

BACKGROUND

Multiple myeloma is a haematological malignancy characterised by neoplastic proliferation of plasma cells, mainly contained within the bone marrow⁴. It is the 17th most common cancer in the UK, accounting for 1% of all cancers and approximately 10% of all haematological malignancies⁵.⁶. Myeloma cells derive from antibody-producing B-cells, this results in a corresponding reduction in the number of normal white blood cells, red cells, and platelets⁷.⁸.
The condition is characterised by the presence of non-functional monoclonal immunoglobulins in serum, urine, or both. Resulting symptoms of multiple myeloma include anaemia, impaired renal function, recurrent or persistent bacterial infection, hypercalcaemia, bone disease, and hyperviscosity.

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:

**CLINICAL NEED and BURDEN OF DISEASE**

The annual incidence of myeloma in the UK is approximately 60-70 per million population. Multiple myeloma is most commonly diagnosed in older people, with 43% of those diagnosed aged 75 years and older, and only 15% of patients aged less than 60 years. The condition is also more frequently diagnosed in men than in women, and the incidence is also reported to be higher in people of African and Caribbean origin. In 2013, 4,703 people were diagnosed with multiple myeloma (ICD-10 C90) in England; in the same year there were 2,449 deaths from multiple myeloma in England and Wales. In 2013-14, there were 108,369 hospital admissions with a primary diagnosis of multiple myeloma (ICD-10 C90.0) in England, resulting in 91,531 bed days and 112,155 finished consultant episodes.

Almost half of patients with myeloma in England and Wales now survive their disease for at least 5 years. The pattern of disease is typically remission followed by relapse requiring further therapy, with research indicating that in Europe approximately 38% of patients will receive 3 or more lines of therapy. With each relapse, the following remission is usually shorter than the previous one. Relapses become more difficult to treat due to the development of drug resistance and the emergence of bone, renal, and haematological problems, which are part of the disease. Patients whose disease has become refractory to bortezomib and immunomodulatory drugs typically have an overall survival (OS) of 9 months, but only 3 months if they receive no therapy following relapse. In 2009, it was estimated that 39% of patients with multiple myeloma had relapsed disease and 65% of patients with relapsed multiple myeloma had received two or more prior therapies.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**
- NICE technology appraisal in development. Multiple myeloma (relapsed, refractory) – carfilzomib (after prior therapy) (ID677). Expected date of issue to be confirmed.
 Horizon Scanning Research & Intelligence Centre

- NICE technology appraisal in development. Panobinostat for treating multiple myeloma in people who have received at least one prior therapy (ID663). Expected January 2016.
- NICE technology appraisal. Pomalidomide for treating relapsed and refractory multiple myeloma previously treated with both lenalidomide and bortezomib (TA338). March 2015.
- NICE technology appraisal. Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy (TA171). June 2009.

Other Guidance

- European Society for Medical Oncology. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2013.

CURRENT TREATMENT OPTIONS

Supportive care plays an important role in the management of multiple myeloma as despite modern treatments significantly improving overall and progression free survival, the vast majority of patients remain incurable. Treatment regimens for multiple myeloma are patient specific and dependent on performance status, eligibility for high dose chemotherapy with stem cell transplantation support, and frailty. Induction therapy followed by high-dose melphalan and autologous stem cell transplantation (ASCT) provides the greatest chance of prolonged survival and complete remission; however this typically only improves survival by up to a year. This treatment is also limited to patients who are able to tolerate it; in Europe, ASCT is primarily offered to patients less than 65 years of age, and is usually only considered in the absence of any serious heart, lung, renal and liver dysfunction. As the median age at diagnosis is 65 years, expert opinion suggests that approximately 60-70% of newly diagnosed multiple myeloma patients are likely to be ineligible for this therapy. The aim in such patients is to give effective combination therapy, which may include melphalan, prednisolone, and thalidomide; cyclophosphamide, dexamethasone, and thalidomide; or bortezomib, melphalan, and prednisolone.

Treatment options for patients with relapsed or refractory multiple myeloma include hematopoietic cell transplantation, rechallenge of the previous chemotherapy regimen, or a trial of a new regimen. Expert opinion suggests that following first relapse, patients are likely to be offered further combination therapy including:
- Bortezomib and dexamethasone +/- cyclophosphamide.

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* Expert personal opinion.
Lenalidomide in combination with dexamethasone is a treatment option for patients with multiple myeloma who have received two or more prior therapies\(^2^4\). In patients with relapsed or refractory multiple myeloma, lenalidomide can overcome resistance to conventional chemotherapy\(^2^5\) and dexamethasone plus lenalidomide is more effective than either agent alone in refractory multiple myeloma\(^2^6\). Expert opinion suggests that lenalidomide is sometimes used as a second line therapy when bortezomib has been used as first line (accessed via the Cancer Drugs Fund)\(^a\).

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01102426, ADMYRE, APL-C-001-09; plitidepsin in combination with dexamethasone vs dexamethasone alone; phase III.</th>
<th>NCT00229203, APL-B-014-03; plitidepsin alone or in combination with dexamethasone; phase II.</th>
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</thead>
<tbody>
<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Completed, published.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry(^1), manufacturer.</td>
<td>Publication(^2^7), poster(^2^8), trial registry(^2^9), manufacturer.</td>
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<tr>
<td>Location</td>
<td>EU (incl. UK), USA and other countries.</td>
<td>Spain and USA.</td>
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<td>Design</td>
<td>Randomised, active-controlled.</td>
<td>Non-randomised, uncontrolled.</td>
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<tr>
<td>Participants</td>
<td>n=250 (planned); aged ≥18 years; relapsed or refractory multiple myeloma; ≥3 but ≤6 prior therapeutic regimens for multiple myeloma (including induction therapy and stem cell transplant in candidate patients, which will be considered as only one regimen); previously treated with bortezomib- and lenalidomide- (or thalidomide) containing regimens, unless unable to tolerate either of them; Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2; life expectancy ≥3 months; no significant concomitant diseases/conditions; no concomitant medications that include corticosteroids, chemotherapy, or other therapy that is or may be active against multiple myeloma.</td>
<td>n=51; aged ≥18 years; relapsed or refractory multiple myeloma following chemotherapy; life expectancy ≥3 months; ECOG performance status ≤2; participant has the following laboratory values within 14 days before treatment: platelet count ≥50 x10(^9)/L, haemoglobin ≥8.0g/dl, absolute neutrophil count ≥1.0x10(^9)/L, corrected serum calcium &lt;14mg/dL, aspartate transaminase ≤2.5 x the upper limit of normal, alanine transaminase ≤2.5 x the upper limit of normal, total bilirubin ≤1.5 x the upper limit of normal, calculated creatinine clearance ≥40mL/minute; left ventricular ejection fraction within normal limits; no current non-haematological toxicity derived from previous treatments (alopecia and grade &lt;2 sensitive peripheral neuropathy are allowed); no other relevant diseases or adverse clinical conditions.</td>
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<td>Schedule</td>
<td>Randomised to plitidepsin 5mg/m(^2) IV on day 1 and 15 of a 28-day cycle in combination with dexamethasone 40mg orally on days 1, 8, 15 and 22 of a 28-day cycle; or dexamethasone alone on days 1, 8, 15 and 22 of a 28-day cycle.</td>
<td>Participants receive plitidepsin 5mg/m(^2) IV infusion every 2 weeks, patients with suboptimal response to plitidepsin alone (progressive disease or stable disease after three or four plitidepsin cycles) were permitted to add dexamethasone 20mg orally on days 1-4, every two weeks.</td>
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<td>Follow-up</td>
<td>Active treatment until progression or unacceptable toxicity, follow-up 6 months.</td>
<td>Active treatment every 2 weeks until progression or death, follow-up 12 months.</td>
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<td>Primary outcome/s</td>
<td>Progression free survival (PFS).</td>
<td>Objective response rate.</td>
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<td>Secondary outcome/s</td>
<td>Response rate, duration of response, overall survival (OS). No quality of life measurement included in trial outcomes.</td>
<td>Time to progression, PFS, OS, and overall safety. No quality of life measurement included in trial outcomes.</td>
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<td>Key results</td>
<td>The company report that following a comprehensive analysis of safety and efficacy of 60 patients required in the first stage of the trial, the study met the established efficacy threshold (a response rate of at least 30%) and the Independent Data Monitoring Committee recommended the continuation of the study.</td>
<td>Results in patients receiving plitidepsin monotherapy (n=21): partial response (PR), n=1 (5%); minimal response (MR), n=1 (5%); stable disease (SD), n=5 (24%); overall response rate (ORR), 10%. During the second study-phase, 29 additional patients were included and patients with suboptimal response to plitidepsin alone were permitted to add dexamethasone. Results in patients receiving plitidepsin monotherapy: ORR, 21%; PR, n=1 (4.3%); MR n=4 (17%); SD, n=15. Dexamethasone was subsequently added in 19 pts, 18 of them evaluable for efficacy, and response was upgraded as follows: PR, n=2 (11%); MR, n=2 (11%); SD, n=9 (50%). Overall, pooled data of all evaluable patients (n=47) receiving plitidepsin as monotherapy in the two stages: ORR, 15% (2 PR, 5 MR); median time to progression (TTP), 3 months (95%CI 2–5); median OS, 17 months. In pts treated with additional dexamethasone: global ORR, 19% (4 PR, 5 MR); median TTP, 4.7 months (95%CI 3–8); 6 month survival, 82% (95%CI 63–100).</td>
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<td>Adverse effects (AEs)</td>
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<td>Very common (&gt;10%) grade 3 AEs for all treated patients and plitidepsin with dexamethasone groups, respectively: fatigue, 15.7% vs 21.1%; muscle weakness, 10.5% vs 2%; renal failure, 0% vs 10.5%; anaemia, 23.5% vs 15.8%; thrombocytopenia, 13.7% vs 5.3%. Very common (&gt;10%) grade 4 AEs for all treated patients and plitidepsin with dexamethasone groups respectively: anaemia, 5.9% vs 10.5%; thrombocytopenia, 3.9% vs 15.8%.</td>
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<td>Expected reporting date</td>
<td>Study completion date reported as February 2016.</td>
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**ESTIMATED COST and IMPACT**

### COST

The cost of plitidepsin is not yet known. The costs of other selected treatments for multiple myeloma are:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Cost per cycle</th>
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<tr>
<td>Bortezomib (Velcade)</td>
<td>3.5mg IV for nine 6-week cycles. Days 1, 4, 8, 11, 22, 25, 29 and 32 in cycles 1 to 4 and days 1, 8, 22 and 29 in cycles 5 to 9. Expert opinion suggests a maximum of 32 doses is usually administered. Each dose (3.5mg vial) costs £762.38</td>
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<tr>
<td>Lenalidomide (Revlimid)</td>
<td>25mg orally on days 1 to 21 of a 28 day cycle</td>
<td>£4,368 per treatment cycle</td>
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<tr>
<td>Pomalidomide (Imnovid)</td>
<td>4mg orally on days 1 to 21 of a 28 day cycle</td>
<td>£8,884 per treatment cycle</td>
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### IMPACT - SPECULATIVE

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- No impact identified
- Other: there is an urgent need for new therapies for those patients who have failed bortezomib and lenalidomide, as their outcomes are poor, with an estimated median survival of 9 months.  

**Impact on Health and Social Care Services**

- Increased use of existing services
- Decreased use of existing services
- Need for new services
- None identified
- Re-organisation of existing services
- Other:

**Impact on Costs and Other Resource Use**

- Increased drug treatment costs
- Reduced drug treatment costs
- Other reduction in costs:
- Other increase in costs: additional costs for IV administration in clinic. This is a single infusion every 2 weeks, that would be a healthcare resource implication, but this would be no different from the antibodies that are currently being investigated for this patient group. This is an older patient group with many co-morbidities and so regular attendance in a haematology unit is likely to be expected.
- Other: uncertain unit cost compared to existing treatments.
- None identified

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*Expert personal opinion.*
Clinical uncertainty or other research question identified: the clinical trials need to include detailed analysis of tumour cell genomics and perhaps even proteomics, to provide insights into possible biomarkers for response, and clues to mechanism of action. This data will inform how plitidepsin is different and/or complementary to other drugs. Also a phase III trial with dexamethasone only as the control arm is probably not acceptable today, as an increasing number of agents are now licensed in this area, e.g. pomalidomide. The ORR of 15% (that includes a MR) for monotherapy/with dexamethasone in the phase II clinical trial is modest but a definite signal, and the achievement of stable disease in a significant number suggests that further investigation in combination with an established anti-myeloma agent such as bortezomib is warranted. Any proper evaluation of its clinical potential would await the results of combination therapy, including with immunomodulatory drugs (IMiDs)c.

REFERENCES

Horizon Scanning Research & Intelligence Centre


15 NIHR Horizon Scanning Research and Intelligence Centre. Carfilzomib (Kryprolis) for multiple myeloma – third line. September 2012. [http://www.hsc.nihr.ac.uk]


21 NIHR Horizon Scanning Research and Intelligence Centre. Panobinostat (Faridak) for relapsed or refractory multiple myeloma. University of Birmingham, April 2012. [http://www.hsc.nihr.ac.uk/]


24 National Institute for Health and Clinical Excellence. Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy (TA171). London: NICE; June 2009.


