Plitidepsin (Aplidin) in combination with dexamethasone for multiple myeloma – third line

SUMMARY

Plitidepsin (Aplidin) is intended to be used in combination with dexamethasone as third line therapy for the treatment of patients with multiple myeloma (MM). If licensed, it would provide an additional treatment option for this patient group. Plitidepsin is a cyclic depsipeptide identified from the Mediterranean marine tunicate, Aplidium albicans.

MM develops from plasma cells in the bone marrow and is the 17th most common cancer in the UK, accounting for around 1.5% of all new cases. Median survival for MM is approximately 3 to 5 years. In 2011, 2,330 deaths from MM were registered in England and Wales, 86% of which were in people aged 65 and over. The latest prevalence data suggests that at the end of 2006 there were 12,465 patients alive up to 10 years after their diagnosis. In 2009, 4,270 people were diagnosed with MM (ICD-10: C90) in England and Wales, giving a crude incidence rate of 8 per 100,000 population.

Treatment regimens for MM will be patient specific and dependent on performance status, eligibility for high dose chemotherapy with stem cell transplantation support, and frailty. There is no standard treatment option for patients who fail both bortezomib- and lenalidomide-based regimens. Plitidepsin is currently in a phase III clinical trial comparing its effect on MM against dexamethasone. This trial is expected to report in June 2014.
TARGET GROUP

- Multiple myeloma (MM): relapsed or refractory; patients who have received bortezomib and lenalidomide-containing regimens (or thalidomide where lenalidomide is not available) – third line

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 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. Plitidepsin also inhibits elongation factor 1-a, interfering with protein synthesis and induces G1 arrest and G2 blockade. It is administered via intravenous (IV) infusion at 5mg/m² on days 1 and 15 of a 28-day cycle in combination with dexamethasone.

Plitidepsin is currently in phase II trials for liposarcoma, and non-Hodgkin’s lymphoma.

INNOVATION and/or ADVANTAGES

If licensed, plitidepsin would provide an additional treatment option for this patient group.

DEVELOPER

Pharma Mar, S.A.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

MM develops from plasma cells in the bone marrow and is the 17th most common cancer in the UK, accounting for around 1.5% of all new cases. The uncontrolled over-production of abnormal plasma cells in MM results in the production of a large amount of a single clone of abnormal antibody, and a reduction in the number of normal white blood cells, red cells and platelets. This leads to anaemia, repeated infections, bone lesions, hypercalcaemia, kidney damage, fatigue and weight loss.

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to: Improving Outcomes: A Strategy for Cancer (2011).
**CLINICAL NEED and BURDEN OF DISEASE**

In 2009, 4,270 people were diagnosed with MM (ICD-10: C90) in England and Wales, giving a crude incidence rate of 8 per 100,000 population. This represents around 1-1.5% of all cancer diagnoses; however, higher incidences are seen in certain ethnic groups, such as those from black ethnic groups. The risk of developing MM increases with age; the median age of presentation is 70 years, with only 2% of patients under the age of 40 years. In 2010-11, there were 63,541 hospital admissions with a primary diagnosis of MM (ICD10 C90.0) in England, resulting in 66,495 bed days and 79,298 finished consultant episodes. Expert opinion suggests that the incidence of patients requiring fourth-line treatment for MM in England is around 0.75/100,000.

Median survival for MM is approximately 3 to 5 years, though this can increase to a median 7 years with use of intensive therapy in some risk groups. In 2011, 2,330 deaths from MM were registered in England and Wales, 86% of which were in people aged 65 and over. The latest prevalence data suggest that at the end of 2006 there were 12,465 patients alive up to 10 years after their diagnosis.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

- NICE technology appraisal in development. Bortezomib for consolidation therapy after autologous stem cell transplantation for the treatment of multiple myeloma (ID529). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Lenalidomide for the treatment of newly diagnosed multiple myeloma (ID474). Suspended.
- NICE technology appraisal in development. Lenalidomide for the maintenance treatment of multiple myeloma after autologous stem cell transplantation (ID475). Suspended.
- NICE technology appraisal in development. Vorinostat in combination with bortezomib for the treatment of multiple myeloma in people who have received at least one prior therapy (ID501). Suspended.
- NICE technology appraisal. Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy (TA171). 2009.

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*a: Expert personal opinion.*
Other Guidance


EXISTING COMPARATORS and TREATMENTS

Treatment regimens for MM will be patient specific and dependent on performance status, eligibility for high dose chemotherapy with stem cell transplantation support, and frailty. First line treatment typically uses thalidomide-based regimens; second line treatments are bortezomib-based regimens; and third line are lenalidomide-based regimens. There is no standard treatment available for patients who have had both bortezomib- and lenalidomide-refractory myeloma.

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>Source of information</td>
<td>Trial registry; manufacturer.</td>
<td>Trial registry; manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl. UK), Australia and USA.</td>
<td>USA and Spain.</td>
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<tr>
<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); adults ≥18 years; relapsed or refractory MM; previously treated with bortezomib- and lenalidomide- (or thalidomide) containing regimens; life expectancy ≥3 months.</td>
<td>n=51; adults ≥18 years; relapsed or refractory MM following chemotherapy; life expectancy ≥3 months.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to plitidepsin 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 cycle, or dexamethasone alone on days 1, 8, 15 and 22 of a 28-day cycle.</td>
<td>Plitidepsin 5mg/m² IV infusion every 2 weeks, alone or in combination with dexamethasone 20mg for 4 days.</td>
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<td>Follow-up</td>
<td>Active treatment for 2-4 cycles, follow-up 24 months.</td>
<td>Active treatment every 2 weeks until progression or death, follow-up 12 months.</td>
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<tr>
<td>Primary outcome/s</td>
<td>Progression free survival.</td>
<td>Objective response rate.</td>
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<tr>
<td>Secondary outcome/s</td>
<td>Response rate, duration of response, overall survival.</td>
<td>Time to progression, progression free survival, overall survival</td>
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<tr>
<td>Key results</td>
<td>-</td>
<td>For plitidepsin only (n=29) and plitidepsin with dexamethasone (n=18) respectively: treatment failure, 48% vs 17%; stable disease, 41% vs 61%; minimal response, 7% vs 11%; partial response, 3% vs 11%; complete response, 0% vs 0%; time to progression, n=29 2.3 months vs n=18 4.2 months; progression free survival, n=21 2.3 months vs n=8 3.8 months; overall survival, n=21 70% at 6 months,</td>
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<td>Adverse effects (AEs)</td>
<td>53% at 12 months, n=8 76% at 6 months, 61% at 12 months.</td>
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<td></td>
<td>For plitidepsin alone and in combination with dexamethasone respectively: fatigue 75% vs 84%, diarrhoea 29% vs 26%, nausea 45% vs 21%, pyrexia 14% vs 16%, pneumonia 14% vs 11%, respiratory tract infection 14% vs 11%.</td>
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<td>Expected reporting date</td>
<td>June 2014.</td>
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**ESTIMATED COST and IMPACT**

**COST**

The cost of plitidepsin is not yet known.

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

☑ Reduced mortality/increased length of survival □ Reduced symptoms or disability
□ Other □ No impact identified

**Impact on Services**

☑ Increased use of existing services: increased need for hospital visits for IV treatment □ Decreased use of existing services
□ Re-organisation of existing services □ Need for new services
□ Other □ None identified

**Impact on Costs**

☑ Increased drug treatment costs □ Reduced drug treatment costs
□ Other increase in costs □ Other reduction in costs
□ Other □ None identified

**Other Issues**

□ Clinical uncertainty or other research question identified ☑ None identified

**REFERENCES**


15 National Institute for Health and Care Excellence. Vorinostat in combination with bortezomib for the treatment of multiple myeloma in people who have received at least one prior therapy. Technology appraisal in development. Suspended May 2012.


