Vorinostat (Zolinza) for cutaneous T-cell lymphoma – second line

January 2008

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Vorinostat (Zolinza) for cutaneous T-cell lymphoma – second line

Target group
- Cutaneous T-cell lymphoma (CTCL); progressive, persistent or recurrent; refractory to prior therapies – second line.

Background
CTCL is one of the many types of indolent or low-grade non-Hodgkin's lymphomas (NHL). The cause of CTCL is unknown, but it results from errors in the transformation of T-lymphocytes into malignant cells, leading to uncontrolled growth and proliferation of malignant T-lymphocytes which accumulate in the skin. In the advanced stage, malignant lymphocytes may spread to affect the lymph nodes and to other tissues and organs.

The prognosis of CTCL depends on how widespread the disease is. If more than 10% of skin is affected, or if the lymphoma has spread to the lymph nodes or organs; the disease is unlikely to be cured. Low-grade NHLs are currently incurable at advanced stages, with a median survival of 8 to 10 years.

Symptoms specific to CTCL include itchiness, dry patches of skin, plaques and tumours on the skin. In the advanced stage, large areas of skin can become reddened and painful, with swollen lymph nodes, liver or spleen.

Technology description
Vorinostat is an oral, small-molecule nanomolar inhibitor of histone deacetylase (HDAC) which has been shown to increase acetylation of core histone proteins (H2A, H2B, H3 and H4) and restore expression of tumour suppressor and/or cell cycle regulatory genes, inducing cell-cycle arrest and apoptosis in a range of cancer cell lines including CTCL.

Vorinostat is being developed as a substitute and as an addition to other therapies when standard treatment has failed. Vorinostat is administered at 400 mg once daily with food. For patients who cannot tolerate this dose, it may be reduced to 300 mg once daily and if necessary, to 300 mg once daily for 5 consecutive days a week. It is intended that treatment with vorinostat will be initiated at a specialist centre.

Vorinostat has US orphan drug status for the treatment of multiple myeloma (MM). Vorinostat is in phase II clinical trials for peripheral T-cell lymphoma and in patients with recurrent or metastatic squamous cell cancer of the head and neck.

Innovation and/or advantages
Vorinostat is the first in a new drug class and is anticipated to be effective in late-stage CTCL with longer duration of response and less toxicity than standard treatment.

Developer
Merck Sharp & Dohme Ltd.

Place of use
- Select one:
  - □ Home care
  - □ Community or residential care e.g. district nurses, physio
  - □ Primary care e.g. used by GPs or practice nurses
  - □ Secondary care: for follow-up care
  - □ Tertiary care e.g. highly specialist cancer centre
  - □ Emergency care e.g. paramedic services, trauma care
  - □ General public e.g. over the counter
  - □ Other:
Availability, launch or marketing dates, and licensing plans:
Vorinostat has orphan drug status for CTCL in the EU and USA.

NHS or Government priority area:
This topic is relevant to the NHS Cancer Plan.

Relevant guidance

Clinical need and burden of disease
CTCL is considered a rare disease with an incidence of 0.4 per 100,000 population per year, however, because most are low-grade malignancies with long survival the overall prevalence is higher. CTCL accounts for approximately 1 in 20 of all cases of NHL. NHL represents approximately 4% of all cancers diagnosed in the UK, with 8,841 new cases registered (an estimated 450 being CTCL) and 3,929 registered deaths, in England and Wales in 2005. CTCL most often occurs in people aged between 40 and 60 and is twice as common in men than women.

Existing comparators and treatments
A number of treatment options can be used for CTCL either alone or in combination; the choice depending on how much of the skin is affected:
- Skin directed therapy (SDT): such as psoralen ultraviolet light A (PUVA), or photochemotherapy, for large affected areas of the skin; and ultraviolet light B (UVB), to slow down growth of skin cells.
- Radiotherapy: for early-stage CTCL if only one or two small areas of skin are affected but may also be used at more advanced stages for plaques and tumours.
- Electron beam therapy (EBT): radiotherapy to treat the whole skin surface if the lymphoma is more widespread, but has not penetrated below the skin surface. It is given once and may be followed up with further PUVA treatment.
- Chemotherapy for advanced CTCL includes: chlorambucil, methotrexate and etoposide, and iv purine analogues 2-deoxycoformycin and 2-chlorodeoxyadenosine.
- Other therapies such as: bexarotene and interferon alfa.

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial name or code</th>
<th>Persistent, progressive or refractory CTCL; Phase IIb</th>
<th>Advanced (stage IIb), refractory CTCL; Phase II.</th>
<th>NCT00419367. Compassionate use for advanced CTCL; Phase III.</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Cutaneous Lymphoma Treatment and research Center at Duke University Medical Center.</td>
<td>MD Anderson Cancer Center, Texas; Merck</td>
<td>Merck</td>
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<tr>
<td>Status</td>
<td>Published8</td>
<td>Published9</td>
<td>Ongoing</td>
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<td>Location</td>
<td>USA</td>
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<td>South America, Europe.</td>
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<tr>
<td>Design</td>
<td>Non-randomised, single arm, open-label.</td>
<td>Non-randomised, open label, uncontrolled.</td>
<td>Non-randomised, open label, uncontrolled.</td>
</tr>
<tr>
<td>Participants in trial</td>
<td>n=74; &gt;18 years; median age: 60 years, range 39-83; stage &gt;Ib CTCL (n=61 stage)</td>
<td>n=33; &gt;18 years; median age was 67 years; received median of 5 prior therapies.</td>
<td>n=100; &gt;18 years; advanced CTCL, previously treated with</td>
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</table>
### Vorinostat (Xeloda) in Recurrent/Refractory IIb Disease

**Primary therapy for group 2:**
- Vorinostat 400 mg orally once daily or
- 300 mg daily for 5 consecutive days per week.

**Secondary therapies:**
- Group 1 - 400 mg daily.
- Group 2 - 300 mg twice daily for 3 days, with 4 days rest for 4 weeks and then 5 days a week.
- Group 3 - 300 mg twice daily for 14 days, with 7-day rest followed by 200 mg twice daily. Continued until disease progression or intolerable toxicity.

**Follow-up:**
- 1 year
- 2 years

**Primary outcome**
- Objective response rate (ORR)
- Complete or partial response (CR, PR)
- Response, safety and efficacy

**Secondary outcomes**
- Time to response (TTR), time to progression (TTP), duration of response (DOR), pruritus relief, safety and tolerability.

**Key results**
- ORR was 30%. Median TTR for stage IIb or higher was 56 days. Median DOR was not reached, but estimated to be 185 days. Median TTP was 4.9 months overall (9.8 months for stage IIb or higher). 32% had pruritus relief, with 43% of those with most severe pruritus.
- 8 achieved PR. Median TTR, DOR and TTP were 11.9, 15.1 and 30.2 weeks respectively. 14 of 31 evaluable patients had pruritus relief.

**Expected reporting date**
- Expected completion: April 2011.

**Adverse effects**
- Mild to moderate in severity: diarrhoea (49%), fatigue (46%), nausea (43%) and anorexia (26%).
- Most common: fatigue, thrombocytopenia, diarrhoea and nausea.

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**Estimated cost and cost impact**

The cost of vorinostat has yet to be determined.

**Potential or intended impact – speculative**

**Patients**
- Reducing morbidity
- Reduced mortality or increased survival
- Quicker, earlier or more accurate diagnosis or identification of disease
- Other:
- Improved quality of life for patients and/or carers
- None identified

**Services**
- Increased use
- Service reorganisation required
- Staff or training required
- Decreased use
- Other:
- None identified

- Other: None identified
Costs

- Increased unit cost compared to alternative
- Increased costs: more patients coming for treatment
- Increased costs: capital investment needed
- New costs:
- Savings:
- Other:

References