Tetrodotoxin for moderate to severe, inadequately controlled cancer-related pain

LAY SUMMARY

Cancer-related pain can arise from both ongoing tissue damage and treatments such as surgery or radiotherapy. Many patients use opioid-based pain killers to manage cancer-related pain but often they do not have complete pain relief.

Tetrodotoxin is a new drug that blocks pain transmission. It is reported to be a well-tolerated, more potent analgesic than aspirin and morphine, and a non-addictive alternative to opioids.

If licensed, tetrodotoxin will offer an additional treatment option for patients with cancer-related pain who may have few, well-tolerated and effective therapies.

NIHR HSRIC ID: 5173
TARGET GROUP

- Cancer-related pain: moderate to severe; inadequately controlled.

TECHNOLOGY

DESCRIPTION

Tetrodotoxin (Halneuron; TTX, 9401-TTX; Tectin; Tetrodin; Tocudin) is a selective blocker of sodium channels found in nerve cells, which produces analgesia either by decreasing the propagation of action potentials by sodium channels and/or by blocking of ectopic discharges associated with chronic pain. Tetrodotoxin is reported to be a more potent analgesic than standard analgesic agents such as aspirin, morphine, or meperidine. In the phase III clinical trial, tetrodotoxin was administered subcutaneously at 30µg twice daily for 4 days.

Tetrodotoxin does not currently have Marketing Authorisation in the EU for any indications. It is in phase II clinical trials for chemotherapy induced neuropathic pain.

INNOVATION and/or ADVANTAGES

If licensed, tetrodotoxin will offer an additional treatment option for patients with cancer-related pain who may have few, well-tolerated and effective therapies.

DEVELOPER

WEX Pharmaceuticals Inc.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Cancer-related pain can arise from both ongoing tissue damage (nociceptive pain) and by nervous system dysfunction with loss of sensation and function (neuropathic pain). Pain from cancer, especially bone metastases, can also have ischaemic and inflammatory components, and pain can be associated with treatments including: chemotherapy, radiation and surgery.

CLINICAL NEED and BURDEN OF DISEASE

It is estimated that around 60% of patients with any stage of cancer and most patients with advanced disease experience significant pain. In hospitalised patients with advanced cancer, nearly 80% experience pain, with 46% having severe pain in spite of their pain relieving treatment. Up to 50% of patients having surgery, chemotherapy and/or radio-

* Company comments.
therapy experience persistent pain and the World Health Organization (WHO) estimates that 25% of patients with cancer die with unrelieved pain\textsuperscript{3,6,7}. Cancer pain can be under-reported and under-treated for many reasons including inadequate education of healthcare professionals in pain management, inadequate pain assessment, reluctance to prescribe opioids, unavailability of analgesics and regulatory barriers\textsuperscript{2,3}. Within the UK, approximately 30% of patients are estimated to receive poor pain control especially in the last years of their lives, representing up to 46,020 patients each year\textsuperscript{3,6}. The company estimates that 1 in 4 patients using opioids to manage cancer-related pain does not receive complete relief from pain\textsuperscript{5}. In addition to this unmet medical need, the number of patients diagnosed with cancer continues to grow\textsuperscript{6}.

In 2014, 296,863 patients, were newly diagnosed with cancer in England\textsuperscript{8}, and 147,000 people died from cancer in England and Wales\textsuperscript{9}. The population likely to be eligible to receive tetrodotoxin, could not easily be estimated from available routine published sources.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**


**NHS England Policies and Guidance**


**Other Guidance**

- Scottish Intercollegiate Guidelines Network. Control of pain in adults with cancer (SIGN 106). 2008\textsuperscript{10}.
- The British Pain Society. Cancer pain management. 2010\textsuperscript{6}.
CURRENT TREATMENT OPTIONS

Patients with pain should have a detailed pain history taken that considers provocative and palliative factors for the pain; its quality (burning/stabbing); its region and pattern of referral; its severity and intensity (assessed using pain relating scales); and temporal factors such as onset, frequency and daily variation.

Although analgesia can be considered for individuals in a step-wise ladder\textsuperscript{7,12} with escalation of treatment from non-opioid analgesia, it is now accepted practice to determine the level and type of analgesia based on the experienced level of pain.

Treatment options include single and combination therapy with\textsuperscript{11}:
- Acetaminophen, aspirin or non-steroidal anti-inflammatory drugs (NSAIDs).
- Immediate-release opioids — codeine, dihydrocodeine, tramadol or propoxyphene.
- Oral and transdermal opioids — morphine, methadone, oxycodone, hydromorphone, fentanyl, alfentanil, buprenorphine, heroin, levorphanol and oxymorphone.

Specific therapies used in neuropathic pain, pain from metastases or other unrelieved pain include\textsuperscript{2}:
- Antidepressants, anticonvulsants, benzodiazepines, neuroleptics, psychostimulants.
- Local and regional anaesthetics.
- Calcitonin and bisphosphonates.
- Chemotherapy and radiation therapy.
- Surgery and neurosurgery.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT00725114,TEC-006; tetrodotoxin vs placebo; phase III.</th>
<th>NCT00726011,TEC-006OL; tetrodotoxin vs placebo; phase III extension.</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Wex Pharmaceuticals Inc.</td>
<td>Wex Pharmaceuticals Inc.</td>
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<tr>
<td>Status</td>
<td>Completed.</td>
<td>Completed.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Poster\textsuperscript{1}, trial registry\textsuperscript{13}.</td>
<td>Trial registry\textsuperscript{14}.</td>
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<tr>
<td>Location</td>
<td>Canada, Australia and New Zealand.</td>
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<td>Design</td>
<td>Randomised, placebo-controlled.</td>
<td>Open-label extension.</td>
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<tr>
<td>Participants</td>
<td>n=165; age ≥18 yrs old; inpatient or outpatient with a diagnosis of cancer; stable but inadequately controlled pain with current therapy for at least two weeks; baseline pain intensity, as assessed by Brief Pain Inventory (BPI) ‘moderate’ (score of 4-5) or ‘severe’ (score of 6-10).</td>
<td>n=113; age ≥18 yrs old; pts who participated in the TEC-006 study; ongoing inadequately controlled pain: pain intensity described as ‘moderate’, ‘severe’ or ‘excruciating’ as assessed during the screening/baseline period of the first treatment cycle, and pain intensity score of ≥4 as assessed by numerical rating scale (NRS); no more than 14 days since the end of TEC-006 visit or pain returned to baseline since their last tetrodotoxin treatment cycle; has not completed 4 cycles of tetrodotoxin.</td>
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<td>Schedule</td>
<td>Randomised to 30µg subcutaneous tetrodotoxin or placebo administered twice daily for 4 days.</td>
<td>Received or continue to receive tetrodotoxin 30µg twice daily for 4 days; repeated every two weeks for as long as there is a meaningful analgesic response.</td>
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### Follow-up
- 15 days or more.
- Every 2 wks as long as there is a meaningful analgesic response.

### Primary outcome/s
- Efficacy: composite-endpoint combining pain outcome and quality of life; pain intensity used as a co-primary endpoint.
- Long term efficacy in reducing pain and improving quality of life.

### Secondary outcome/s
- Duration and length of pain response.
- Number of days of pain response.

### Key results
- Analysis on all completed 149 pts, for TTX vs placebo, respectively:
  - % QoL plus composite endpoint, 29.2 vs 20.2 (p=0.203); % pain responder, 50.8 vs 34.5 (p=0.046), significant at the one-sided 5% level but not at the pre-specified two-sided 5% level.
  - Duration of analgesic response: the median duration of pain response was 12 days with TTX vs 8 days for placebo (p=0.0345). There were more long duration responders in the TTX group.

### Adverse effects (AEs)
- Most common AEs: nausea, dizziness, oral hypoesthesia, hypoesthesia, oral paresthesia, vomiting, and injection site irritation. Serious AEs related to TTX (after unblinding): 5 events from 3 pts: cerebral ataxia, neurotoxicity, ataxia, nystagmus, and aspiration pneumonia. Most treatment-emergent adverse events were mild to moderate, transient, self-limiting, and managed with standard supportive care.

### ESTIMATED COST and IMPACT

#### COST
The cost of tetrodotoxin 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 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: expert opinion suggests that effective treatment of these patients may result in some resource saving.
- Other
- None identified

Other Issues

- Clinical uncertainty or other research question identified: an expert states that there is an unmet need in intractable cancer pain. Tetrodotoxin would likely be a treatment reserved for use after failure of the stepped analgesic ladder approach, unless side effect profile was low, and cost low.
- None identified

REFERENCES


b Expert personal opinion.