Dexpramipexole for amyotrophic lateral sclerosis

SUMMARY

Dexpramipexole (BIIB 050, KNS-760704) is intended to be used for the treatment of amyotrophic lateral sclerosis (ALS). ALS, which is sometimes referred to as Lou Gehrig disease, is characterised by both upper and lower motor neuron damage, where mutations in several genes and environmental factors have been implicated. If licensed, dexpramipexole will offer an additional treatment for ALS patients, who currently have limited effective therapeutic options. Dexpramipexole is a small molecule, synthetic benzothiazole compound. Its exact mode of action is unknown, but it is believed to have a neuroprotective effect on neurons when under stress by promoting mitochondrial function within motor neuron cells. It is not currently licensed for any other indication.

ALS is the most common form of motor neuron disease (MND), accounting for 65% to 85% of all cases. The incidence of ALS ranges from 1.8 to 2.2 per 100,000 population and its prevalence ranges from 4.0 to 4.7 per 100,000 population in the UK. In England there were 2,722 admissions for MND, resulting in 26,947 bed days and 3,877 finished consultant episodes in 2010-11. In 2010, there were 1,941 deaths registered from MND in England and Wales.

A range of pharmacological interventions are available to provide symptomatic relief for people with MND but Riluzole (Rilutek) is currently the only drug licensed to treat ALS in the UK. Dexpramipexole is currently in two phase III clinical trials comparing its effect on functional outcomes adjusted for mortality and safety, against treatment with placebo. These trials are expected to complete between 2013 and 2016.
TARGET GROUP

- Amyotrophic lateral sclerosis (ALS).

TECHNOLOGY

DESCRIPTION

Dexpramipexole (BIIB 050; KNS-760704) is a small molecule, synthetic benzothiazole compound. Its exact mode of action is unknown, but it is believed to have a neuroprotective effect on neurones when under stress by promoting mitochondrial function within motor neurone cells. Dexpramipexole is intended to be used for the treatment of ALS, and is administered orally at 150mg twice daily as monotherapy and/or add-on therapy.

INNOVATION and/or ADVANTAGES

If licensed, dexpramipexole will offer an additional treatment for ALS patients, who currently have limited effective therapeutic options.

DEVELOPER

Biogen Idec.

PATIENT GROUP

BACKGROUND

Motor neurone disease (MND) is characterised by progressive degeneration of the motor neurones of the brain, brain stem and spinal cord. The term ‘Motor Neurone Disease’ is usually used to describe certain variants of the disease, including ALS, progressive muscular atrophy (PMA), and primary lateral sclerosis (PLA). ALS, which is sometimes referred to as Lou Gehrig disease, is characterised by both upper and lower motor neurone damage. Mutations in several genes and environmental factors have been implicated in ALS, which influence cellular processes involving free radical damage, mitochondrial impairment, abnormal protein precipitation, and abnormal cellular trafficking pathways.

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to The Long-Term (Neurological) Conditions National Service Framework (2005).

CLINICAL NEED and BURDEN OF DISEASE

ALS is the most common form of MND, accounting for 65% to 85% of all cases. The incidence of ALS ranges from 1.8 to 2.2 per 100,000 population and its prevalence ranges from 4.0 to 4.7 per 100,000 population in the UK. At any one time, there are about 2,000 individuals per year in England and Wales affected by ALS. In England there were 2,722...
admissions for MND (ICD10 G12.2), resulting in 26,947 bed days and 3,877 finished consultant episodes in 2010-11\(^5\). In 2010, there were 1,941 deaths registered from MND (ICD10 C64-66, C68) in England and Wales\(^6\).

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

- NICE clinical guideline. Motor Neurone Disease – the use of non-invasive ventilation in the management of motor neurone disease. 2010\(^7\).
- NICE technology appraisal. Riluzole (Rilutek) for the treatment of Motor Neurone Disease. 2001\(^8\).

**Other Guidance**

- Royal College of Physicians. Long-term neurological conditions: management at the interface between neurology, rehabilitation and palliative care. 2006\(^9\).

**EXISTING COMPARATORS and TREATMENTS**

A range of pharmacological interventions are available to provide symptomatic relief for people with MND. Surgical intervention may also be necessary, including percutaneous gastrostomy to enable feeding as the ability to swallow decreases, and support to aid breathing as respiratory muscles weaken\(^3\). Riluzole (Rilutek) is currently the only drug licensed to treat ALS in the UK\(^3\) (the licensed indication of riluzole is to extend life or the time to mechanical ventilation for individuals with ALS\(^3\)); expert opinion suggests that this has only a modest effect on survival\(^a\).

**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
<th>Source of information</th>
<th>Location</th>
<th>Design</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01281189, 223AS302, EUDRA CTA NO: 2010-022818-19; dexpramipexole vs placebo; phase III.</td>
<td>Biogen Idec.</td>
<td>Ongoing.</td>
<td>Trial registry(^a).</td>
<td>EU (inc UK), USA, Canada and other countries.</td>
<td>Randomised, placebo-controlled.</td>
<td>n=943 (planned); adults; familial or sporadic ALS.</td>
</tr>
<tr>
<td>ENVISION, NCT01622088, 223AS304; dexpramipexole; phase III extension.</td>
<td>Biogen Idec.</td>
<td>Ongoing.</td>
<td>Trial registry(^a).</td>
<td>EU (inc UK), USA, Canada and other countries.</td>
<td>Uncontrolled, Single-arm.</td>
<td>n=603 (planned); adults; familial or sporadic ALS; completed trial NCT01281189.</td>
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</tbody>
</table>

\(^a\) Expert opinion.
<table>
<thead>
<tr>
<th>Schedule</th>
<th>Randomised to dexpramipexole, oral, 150mg twice daily for up to 18 months or placebo, oral, twice daily for up to 18 months.</th>
<th>Participants receive dexpramipexole, oral, 150mg twice daily for up to 36 months</th>
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<tbody>
<tr>
<td>Follow-up</td>
<td>Active treatment period 12-18 months.</td>
<td>Active treatment period up to 36 months.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>Functional outcomes adjusted for mortality.</td>
<td>Adverse effects (AEs) and serious adverse effects (SAEs), discontinuation of study treatment due to AEs, change in vital signs.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Time to death, respiratory decline, change in ALS-related health quality, change in muscle strength measurements, safety.</td>
<td>Change in ALS functional rating scale (ALSFRS-R), decline in sniff nasal-inspiratory pressure (SNIP), time to death.</td>
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**Trial**
NCT00647296, KNS-760704-CL201; dexpramipexole vs placebo; phase II.

**Sponsor**
Knopp Neurosciences.

**Status**
Completed and published in abstract.

**Source of information**
Trial registry\(^1\) and publication\(^2\).

**Location**
USA.

**Design**
Randomised, placebo-controlled.

**Participants and schedule**
n=102; adults; familial or sporadic ALS.
Part 1; randomised to dexpramipexole 50mg, 150mg, 300mg, or placebo, oral daily for up to 12 weeks.
Part 2; participants who complete all 12 weeks of part 1 are eligible for randomisation in part 2. Randomised to dexpramipexole, oral, 50mg or 300mg daily for at least 24 weeks.

**Follow-up**
Active treatment period 48 weeks.

**Primary outcome/s**
Safety.

**Secondary outcome/s**
Safety, change in ALSFRS-R, change in upright and supine vital capacity, change in cystatin C and neurofilament H.

**Key results**
For placebo, 50mg, 150mg and 300mg groups respectively (part 1): mean ALSFRS-R scores: \(-1.28\) (95% CI, 1.82 to -0.74), \(-1.89\) (95% CI, 2.48 to -1.29), \(-1.17\) (95% CI, 1.71 to -0.62) and \(-0.88\) (95% CI, 1.44 to -0.31).

**Adverse effects (AEs)**
No deaths or treatment related serious adverse effects (SAEs) in part 1. 17 subjects with SAEs in part 2 (23% in the 50mg group and 14% in the 300mg group).

**ESTIMATED COST and IMPACT**

**COST**
The cost of dexpramipexole is not yet known. Riluzole (Rilutek) 50mg twice daily costs £320.33 for 28 days\(^3\).

**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
- 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: new costs – additional treatment option
  - None identified

Other Issues

- Clinical uncertainty or other research question identified: expert opinion suggests that individuals from families with known mutations in ALS genes may present with PMA or PLS patterns of MND rather than ALS. Effectiveness of dexpramipexole for these patterns of MND, requires further study.

None identified

REFERENCES