Innovation Observatory

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EVIDENCE BRIEFING
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Edaravone for amyotrophic lateral sclerosis

NIHRIO ID	12968	**NICE ID**	10090
Developer/Company	Mitsubishi Tanabe Pharma Europe Ltd	**UKPS ID**	649762

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Edaravone as an intravenous injection is in clinical development for people with amyotrophic lateral sclerosis (ALS). ALS is a neurological condition that affects nerve cells in the brain and spinal cord. It results in gradual weakness and wasting of muscles of the body. Respiratory muscles are involved as the disease progresses, leading to shortness of breath and ultimately death. Little is known about the cause of the disease, and there is currently no cure.

Edaravone acts as a free radical scavenger (or antioxidant). Free radicals can occur as a normal part of the cellular process of producing energy and are quickly removed by the body. However, if they remain, they can cause oxidative stress, leading to damage and cell death. Oxidative stress caused by free radicals is believed to be one of the causes of nerve cell death in ALS. Edaravone has a neuroprotective effect and slows the progression of ALS by removing free radicals in the nervous system. If licensed, edaravone will offer an additional treatment option for patients with ALS who currently have few effective therapies available.

PROPOSED INDICATION

Treatment of amyotrophic lateral sclerosis (ALS)[1,2]

TECHNOLOGY

DESCRIPTION

Edaravone (Radicava; MCI-186) is a member of the substituted 2-pyrazolin-5-one class. The exact mechanism of action of edaravone in the treatment of amyotrophic lateral sclerosis (ALS) is unknown, although its therapeutic effect may be due to its known antioxidant properties (oxidative stress is a part of the process that kills neurons in patients with ALS).[3]

Edaravone is currently in clinical development for the treatment of ALS. In the phase III trial (NCT01492686), two ampoules (60mg) of edaravone injection are intravenously administered once a day, for successive 14 days, followed by 14 days observation period (first cycle). Then treatment (10 days' administration during 14 days) - observation (14 days) cycle is repeated five times (2nd-6th cycles).[4]

INNOVATION AND/OR ADVANTAGES

Damage to nerve cells in ALS appears to have several causes but there is evidence that it may involve toxic molecules containing oxygen. In some patients this is associated with a defect in the gene responsible for producing the enzyme called superoxide dismutase (SOD), which causes the enzyme to clump together inside nerve cells. This leads to inflammation and kills the affected nerve cells. Edaravone acts as an antioxidant, a molecule that can prevent damage to nerve cells caused by oxygen-containing molecules, and also to block the clumping together of SOD in the nerves and so reduces inflammation.[5]

Currently, riluzole is the only drug licensed in the EU/UK for the treatment of ALS.[6] Emerging information has shown that edaravone might be of significant benefit for patients with the condition because studies in ALS patients showed favourable effects when edaravone was used in combination with riluzole treatment.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Edaravone does not currently have Marketing Authorisation in the EU/UK for any indication.[7]

Edaravone is in phase III clinical trials for acute ischemic stroke and phase II clinical trials for radiation-induced temporal lobe necrosis.[8]

Edaravone was granted EU orphan drug status by the EMA on 19 June 2015 for the treatment of ALS.[5]

Edaravone was granted US orphan drug status by the FDA on 05 May 2015 for the treatment of ALS.[9]

Edaravone was granted approval by the FDA in May 2017 for the treatment of ALS.[10]

PATIENT GROUP

DISEASE BACKGROUND

Motor neuron diseases (MNDs) are a group of progressive neurological disorders that destroy motor neurons. MNDs are classified according to whether they are inherited or sporadic, and to whether

degeneration affects upper motor neurons, lower motor neurons, or both. In adults, the most common MND is amyotrophic lateral sclerosis (ALS). Many doctors use the terms MND and ALS interchangeably.[11]

ALS, also called Lou Gehrig's disease or classical motor neuron disease, is a type of MND characterised by the progressive degeneration and eventual death of motor neurons in the brain, brainstem, and spinal cord that facilitate communication between the nervous system and voluntary muscles of the body. ALS affects the upper and lower motor neurons causing the bodies' muscles to gradually weaken and waste away leading to respiratory failure due to loss of control of the muscles in the chest and diaphragm.[12]

Causes of ALS include gene mutation (familial), chemical imbalance, disorganised immune response and protein mishandling. A handful of factors have been proposed to be associated with ALS; however, the only established risk factors to date are older age, male sex, and a family history of ALS. A few other factors that have been suggested to be linked with ALS include gene mutations, smoking and higher level of physical fitness with lower body mass index.[13] ALS affects more men than women (60% of cases are in males).[12]

Progressive muscular weakness in ALS presents as isolated and unexplained symptoms which include falls or trips, loss of dexterity, weakened grip, cramps, fasciculation, change in voice quality and speech, awareness of swallowing changes and muscle wasting. Respiratory muscles are involved as the disease progresses, leading to breathlessness and symptoms of hypoventilation. Some people with ALS experience cognitive changes, ranging from mild effects to noticeable impairment while some experience frontotemporal dementia.[14]

Many people with ALS will eventually be completely dependent on others. Cause of death is almost always due to respiratory failure as a consequence of respiratory muscle weakness and/or repeated chest infections.[14]

CLINICAL NEED AND BURDEN OF DISEASE

The incidence of ALS in European populations is 2-3/100,000 of the general population. In Europe, crude prevalence ranges from 1.1/100,000 to 8.2/100,000.[15] If these figures are applied to the 2017 mid-year population estimates for England and Wales, this equates to an incidence of 1,175 – 1,762 and a prevalence of 646 – 4,817.

Around 35% of people with ALS experience mild cognitive change, which can cause issues in executive functions such as planning, decision-making and language a further 5-10% of people with ALS show signs of frontotemporal dementia which results in more pronounced behavioural change.[14]

Survival is usually less than five years from onset of symptom.[13]

According to HES data for England, there were 4,320 finished consultant episodes (FCEs) and 2,641 admissions in 2016-17 for 'motor neuron disease' (G12.2) resulting in 26,853 FCE bed days.[16]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

Management of ALS consists of riluzole for the treatment of ALS and multidisciplinary team assessments that involve evaluation of problems related to muscles, nutrition and gastronomy, psychological and social care, respiratory function, saliva, speech and communication needs, and

support for activities of daily living.[17] Early diagnosis offers the best prognosis for a longer, quality life while living with the disease.[18]

CURRENT TREATMENT OPTIONS

Riluzole should be recommended for all patients with ALS, provided there are no contraindications to its use. Riluzole is recommended for patients with ALS of less than 5 years' duration and forced vital capacity greater than 60%.[18]

PLACE OF TECHNOLOGY

If licensed, edaravone may offer an additional treatment option to patients who have ALS who currently have few effective therapies available.

CLINICAL TRIAL INFORMATION

Trial	**NCT01492686, MCI186-19; subjects aged 20-75 years; edaravone vs placebo; phase III**
Sponsor	Mitsubishi Tanabe Pharma Europe Ltd
Status	Complete
Source of Information	Trial registry,[4] Journal article[19]
Location	Japan
Design	Randomized, placebo-controlled, parallel assignment
Participants	n=137; aged 20-75 years; amyotrophic lateral sclerosis
Schedule	Randomised to two ampoules (60mg) of edaravone injection or two ampoules of placebo injection intravenously administered once a day, for successive 14 days, followed by 14 days observation period (first cycle). Then treatment (10 days' administration during 14 days) – observation (14 days) cycle is repeated five times (2nd-6th cycles).
Follow-up	Active treatment for 6 cycles (up to 24 weeks), follow-up not stated on the trial registry.
Primary Outcomes	Change from baseline in Revised ALS Functional Rating Scale (ALSFRS-R) score at 24 weeks
Secondary Outcomes	• Time to death from date of randomization • Time to a certain state from date of randomization • % Forced Vital Capacity (%FVC) • Modified Norris scale score • Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40 score) • Adverse events, adverse drug reactions, laboratory test and sensory examinations All secondary outcomes were observed at 24 weeks.

Key Results	Assessments of Modified Norris Scale (total) favoured edaravone compared with placebo (least-squares mean difference 4.89, SE 2.35; p=0.0393). Deterioration in quality of life, shown by ALSAQ-40, was lower in patients receiving edaravone compared with patients receiving placebo (least-squares mean difference −8.79, SE 4.03; p=0.0309). There was no difference in FVC, Modified Norris Scale (limb or bulbar), grip strength, pinch strength (table 2), or ALS severity classification at the end of cycle 6 (appendix) in patients given edaravone compared with placebo. Death or a specified state of disease progression occurred in two patients in the edaravone group (one tracheotomy and one loss of useful speech) and in six patients in the placebo group (three loss of useful speech, two disabilities of independent ambulation, and one use of tube feeding). The difference between groups for this secondary endpoint was not significant (log-rank test p=0.13, generalised Wilcoxon test p=0.14).
Adverse effects (AEs)	The number of patients reporting at least one adverse event did not differ significantly between the two groups (58 [84%] of 69 patients in the edaravone group vs 57 [84%] of 68 patients in the placebo group). 11 (16%) of 69 patients in the edaravone group and 16 (24%) of 68 patients in the placebo group encountered at least one serious adverse event.
Expected reporting date	-

Trial	**NCT00330681, MCI186-16; subjects aged 20-75 years; edaravone vs placebo; phase III**
Sponsor	Mitsubishi Tanabe Pharma Europe Ltd
Status	Complete
Source of Information	Trial registry,[1] Journal article[20]
Location	Japan
Design	Randomized, placebo-controlled, parallel assignment
Participants	n=206; aged 20-75 years; amyotrophic lateral sclerosis
Schedule	Randomised to two ampoules (60mg) of edaravone injection or two ampoules of placebo injection intravenously administered once a day, for successive 14 days, followed by 14 days observation period (first cycle). Then treatment (10 days' administration during 14 days) – observation (14 days) cycle is repeated five times (2nd-6th cycles).
Follow-up	Active treatment for 6 cycles (up to 24 weeks), follow-up not stated on the trial registry.
Primary Outcomes	Change from baseline in Revised ALS Functional Rating Scale (ALSFRS-R) score in Full Analysis Set (FAS) population at 24 weeks
Secondary Outcomes	• Death or a specified state of disease progression • Change from baseline in % Forced Vital Capacity (%FVC) in Full Analysis Set (FAS) • Change from baseline in Modified Norris Scale Score in FAS

	• Change from baseline in ALS assessment questionnaire (40 Items) (ALSAQ40) in FAS • Percentage of participants with adverse events • Percentage of participants with adverse drug reactions • Percentage of participants with laboratory tests for which the incidence of abnormal changes was 5% or higher in either group • Percentage of participants with abnormal changes in sensory examinations All secondary outcomes were observed at 24 weeks.
Key Results	The study failed to demonstrate efficacy of edaravone to delay the progression of ALS. While the primary endpoint was not achieved, the company considers that the results are helpful to identify the patient population in which edaravone could be expected to show efficacy.
Adverse effects (AEs)	The proportion of AEs reported in the safety population was 88.5% in the placebo group and 89.2% in the edaravone group. The proportion of SAE was 23.1% in the placebo group and 17.6% in the edaravone group. There were no significant inter-group differences in the proportion of AE or SAE.
Expected reporting date	-

Trial	**NCT00424463, MCI186-17; subjects aged 20-75 years; edaravone vs placebo; phase III extension**
Sponsor	Mitsubishi Tanabe Pharma Europe Ltd
Status	Complete
Source of Information	Trial registry,[2] Journal article[21]
Location	Japan
Design	Randomized, placebo-controlled, parallel assignment
Participants	n=181; aged 20-75 years; amyotrophic lateral sclerosis
Schedule	Randomised to two ampoules (60mg) of edaravone injection or two ampoules of placebo injection intravenously administered once a day, for successive 14 days, followed by 14 days observation period (first cycle). Then treatment (10 days' administration during 14 days) - observation (14 days) cycle is repeated fifteen times (2nd-15th cycles).
Follow-up	Active treatment for 9 cycles over 36 weeks.
Primary Outcomes	Change from baseline in ALSFRS-R score in FAS population at 24 weeks
Secondary Outcomes	• Number of participants with death or a specified state of disease progression [Time frame: 24 weeks (from 7th-12th cycle)] • Change from baseline in % Forced Vital Capacity (%FVC) in FAS population at 24 Weeks [Time frame: baseline (7th cycle) and at 24 week (12th cycle)] • Percentage of participants with adverse events [Time frame: 36 weeks (from 7th cycle to 15th cycle)] • Percentage of participants with adverse drug reactions [Time frame: 36 weeks (from 7th cycle to 15th cycle)]

	• Percentage of participants with laboratory tests for which the incidence of abnormal changes was 5% or higher in either group [Time frame: 36 weeks (from 7th cycle to 15th cycle)] • Percentage of participants with abnormal changes in sensory examinations [Time frame: 36 weeks (from 7th cycle to 15th cycle)]
Key Results	The intergroup difference in ALSFRS-R score between edaravone and placebo was not statistically significant in either the FAS or the efficacy expected sub-population.
Adverse effects (AEs)	The most common AEs (≥10% of patients across all treatment groups) were nasopharyngitis, gait disturbance, constipation, dysphagia, and musculoskeletal disorder. There was no statistically significant difference in the incidence of AEs between the edaravone and the placebo groups. The most common SAEs (> 6% of patients across all treatment groups) were dysphagia and musculoskeletal disorder. There was statistical difference in the incidence of SAEs between the edaravone and the placebo group (p = 0.0344, Fisher's exact test); the incidences were 52.1% (25/48 patients) in the edaravone group and 28.9% (13/45 patients) in the placebo group.
Expected reporting date	-

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Masitinib for treating amyotrophic lateral sclerosis [ID967]. Expected publication date to be confirmed.
- NICE technology appraisal guidance. Guidance on the use of Riluzole (Rilutek) for the treatment of Motor Neurone Disease (TA20). January 2001
- NICE guideline. Motor neurone disease: assessment and management (NG42). February 2016.
- NICE quality standard. Motor neurone disease (QS126). July 2016

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Neurosciences: Specialised Neurology (Adult). D04/S/a
- NHS England. 2013/14 NHS Standard Contract for Specialised rehabilitation for patients with highly complex needs (All ages). D02/S/a

OTHER GUIDANCE

- Motor Neurone Disease Association (MNDA) and Royal College of General Practitioners (RCGP). Motor neurone disease: a guide for GPs and primary care teams. 2018.[14]

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