AWMSG Secretariat Assessment Report – Limited submission

Ataluren (Translarna®▼) 125 mg, 250 mg and 1,000 mg granules for oral suspension

Company: PTC Therapeutics Ltd

Licensed indication under consideration: Ataluren (Translarna®▼) for the treatment of Duchenne muscular dystrophy (DMD) resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 2 years to less than 5 years.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Date of licence extension: 23 July 2018

Comparator(s)

Ataluren (Translarna®) is the first licensed treatment for nonsense mutation DMD in children aged ≥ 2 years to < 5 years. Standard of care management may include corticosteroid treatment.

Limited submission details

The limited submission criteria were met based on a new minor licence extension.

Clinical effectiveness

- Ataluren (Translarna®) has previously been recommended by the National Institute for Health and Care Excellence as a highly specialised technology (HST3) for treating nonsense mutation DMD in children aged five years and older who can walk. The All Wales Medicines Strategy Group (AWMSG) supported the adoption and implementation of this advice within NHS Wales in 2016.
- Nonsense mutation DMD is a rare, progressive muscle-wasting genetic disorder. Symptoms appear by age 3 years, wheelchair dependency between ages 9 and 12 years, and death usually before age 30 years. Standard of care management is palliative and does not treat the underlying cause of the disease.
- The submission includes results from a 28-day, phase II, multiple-dose, open-label study (Study 030), conducted in the USA, to evaluate the safety, pharmacokinetics and pharmacodynamics of ataluren in 14 ambulatory patients aged ≥ 2 years to < 5 years with nonsense mutation DMD and body weight ≥ 12 kg. A 48-week extension phase collected longer-term safety and functional endpoint data. Pharmacokinetics results showed that in patients aged ≥ 2 years to < 5 years ataluren plasma concentrations after 28 days of treatment were consistent with those observed in patients aged ≥ 5 years.

- The extension phase of Study 030 assessed muscle function of patients at Week 28 using three tests (time to walk or run 10 m; time to climb four stairs; and time to stand up from lying down) and an eight-item North Star Ambulatory Assessment. Comparing the results with those of historical controls (n = 10–31) showed a trend favouring ataluren. The Committee for Medicinal Products for Human Use (CHMP) concluded that the efficacy of ataluren in children aged ≥ 2 years to < 5 years is expected to be similar to that in children aged ≥ 5 years.
- In Study 030 the safety profile of ataluren in children aged ≥ 2 to < 5 years appeared similar to that observed in children aged ≥ 5 years. Reported adverse events were mild to moderate and were in line with those reported in children aged ≥ 5 years. All 14 patients entered the extension study and none have discontinued treatment early. The CHMP concluded that the safety of ataluren in children aged ≥ 2 to < 5 years is expected to be similar to that in children aged ≥ 5 years; there were no new safety concerns. There are no long-term safety data.

Budget impact

- [commercial in confidence text removed]
- The company calculated an estimated incidence of one new eligible child every three years using published DMD incidence data for Wales, published DMD mutation-type data and 2017 Welsh birth statistics.
- The company assumes [commercial in confidence text removed] in Year 1 and calculates one eligible child in Year 5 based on the estimated incidence of nonsense mutation DMD and taking into account children transferring to the currently funded ≥ 5 years age group within the five-year timeframe.
- The cost of ataluren treatment depends on a person's weight. The company calculates that the annual treatment cost for a child aged ≥ 2 years to < 5 years, based on a Patient Access Scheme (PAS) discount price for ataluren, is between [commercial in confidence figure removed].
- Using the PAS discount price and there being [commercial in confidence text removed] in Year 1 and one in Year 5, the company estimates the budget impact is [commercial in confidence figure removed] in Year 1 and [commercial in confidence figure removed] in Year 5, calculated for a three-year-old child of average weight (15–16 kg).

Consideration of AWMSG policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases

- The European Medicines Agency granted ataluren (Translarna®) orphan status in 2005. The prevalence of DMD in the UK is estimated at 2.48 in 100,000 people. Nonsense mutations are reported to be present in 10% of people with DMD. This equates to eight people with nonsense mutation DMD in Wales.
- The All Wales Therapeutics and Toxicology Centre considers ataluren eligible to be appraised as an ultra-orphan medicine as the full population of the licensed indication does not exceed the threshold of ≤ 1 in 50,000 in the UK (or ≤ 60 patients in Wales). The New Medicines Group and AWMSG will consider additional criteria (see Table 1) if they consider ataluren as an ultra-orphan medicine.

Table 1. Evidence considered by NMG/AWMSG

NMG/AWMSG Considerations	AWTTC Comments
The degree of severity of the disease as presently managed, in terms of survival and quality of life impacts on patients and their carers.	DMD is a severe genetic disorder causing progressive muscle degeneration and weakness due to lack of dystrophin. It mainly affects boys. Symptoms appear by the age of 3 years. Children with DMD lose motor function until eventually they become wheelchair dependent, usually between the ages of 9 and 12 years. As the disease progresses, people with DMD lose the ability to breathe unaided and need assisted ventilation. Scoliosis develops as the back muscles weaken, for which surgery is needed. Progressive respiratory and cardiac failure lead to death, usually before the age of 30 years. DMD has a substantial impact on the quality of life of people with the condition and their families, particularly after a person loses their ability to walk which is usually followed by greater deterioration in muscle function. After this point, people with DMD need almost constant care to perform routine daily activities.
Whether the medicine addresses an unmet need (e.g. no other licensed medicines)	Currently, only people with nonsense mutation DMD who are aged ≥ 5 years can access ataluren treatment in NHS Wales. Children aged ≥ 2 to < 5 years with nonsense mutation DMD have no therapy options that treat the underlying cause of the disease. Current treatments are aimed at alleviating symptoms and managing complications. These include treatment with corticosteroids (not licensed to treat DMD) which temporarily increase muscle strength and function but can also have significant side effects. The company states that because dystrophin production is affected from birth and symptoms of DMD usually appear between the ages of 1 and 3 years, it is critical that disease-modifying therapy is started early, to maximise the potential benefit of treatment.
Whether the medicine can reverse or cure, rather than stabilise the condition	Ataluren cannot reverse or cure nonsense mutation DMD.
Whether the medicine may bridge a gap to a “definitive” therapy (e.g. gene therapy) and that this “definitive” therapy is currently in development	There is no other definitive therapy available. Phase I and phase II studies of gene therapies for nonsense mutation DMD are under way.
The innovative nature of the medicine	Ataluren is the first licensed medicine to treat the underlying cause of nonsense mutation DMD. The EMA’s review concluded that ataluren offered therapeutic innovation and clinically relevant benefits for a rare disease with high unmet need.
Added value to the patient which may not adequately be captured in the QALY (e.g. impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity)	A cost-effectiveness evaluation of children aged 2–5 years with nonsense mutation DMD has not been conducted. The company states that because ataluren delays functional decline in patients with nonsense mutation DMD, it expects that treatment with ataluren will enable them to continue in education and to maintain their independence and dignity for longer. Parents and carers of people with DMD say it’s important that the person can keep walking for as long as possible, because loss of walking ability indicates disease progression.
Added value to the patient’s family (e.g. impact on a carer or family life)	The company referred to published studies describing the impact on families of caring for a child with DMD. Parents report a high burden of care for their child from an early age but they experience the greatest emotional impact when their child loses their ability to walk. As the disease progresses people with DMD need more and more full-time care. This means that parents, guardians and carers are unable to continue with their usual employment and social life.
AWMSG: All Wales Medicines Strategy Group; AWTTC: All Wales Therapeutics and Toxicology Centre; DMD: Duchenne muscular dystrophy; EMA: European Medicines Agency; NMG: New Medicines Group; QALY: quality-adjusted life-year.	

Additional information

- AWTTC is of the opinion that, if recommended, ataluren (Translarna®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.
- The company anticipates that ataluren (Translarna®) will be supplied by a home healthcare provider using arrangements already in place.

Evidence search

Date of evidence search: 5 November 2018.
Date of range of evidence search: No date limits were applied to database searches.

Further information

This assessment report will be considered for review every three years.

References are available on request. Please email AWTTC at AWTTC@Wales.nhs.uk for further information.

This report should be cited as: All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Ataluren (Translarna®) 125 mg, 250 mg and 1,000 mg granules for oral suspension. Reference number: 3911. February 2019.