ataluren 125mg, 250mg, 1,000mg granules for oral suspension (Translarna®) SMC No. (1131/16)
PTC Therapeutics Ltd

04 March 2016

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission considered under the ultra-orphan process

ataluren (Translarna®) is not recommended for use within NHS Scotland.

**Indication under review:** Treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older.

In a phase IIb, randomised, double-blind study the absolute difference in mean change in 6-minute walking distance from baseline to week 48 for ataluren 40mg/kg/day compared to placebo was 30 metres in the intent-to-treat analysis.

The submitting company’s justification of the treatment’s cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium
**Indication**
Treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older. Efficacy has not been demonstrated in non-ambulatory patients.

The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing.

**Dosing Information**
Ataluren should be administered orally every day in three doses. The recommended dose is 10mg/kg body weight in the morning, 10mg/kg body weight at midday, and 20mg/kg body weight in the evening (for a total daily dose of 40mg/kg body weight). Ataluren should be administered orally after mixing it to a suspension in liquid or in semi-solid food.

Treatment with ataluren should only be initiated by specialist physicians with experience in the management of Duchenne/Becker muscular dystrophy.

**Product availability date**
September 2014.
Ataluren has conditional marketing authorisation from the European Medicines Agency (EMA). Ataluren meets SMC ultra-orphan criteria and has been designated an orphan medicine by the EMA.

**Summary of evidence on comparative efficacy**

Duchenne muscular dystrophy is a rare X-linked genetic condition caused by mutations in the gene for dystrophin. This protein is essential to the structural stability of myofibres in skeletal, diaphragmatic and cardiac muscle and is also of importance for the central nervous system and smooth muscles. Around 10% of patients with Duchenne muscular dystrophy will have the nonsense mutation. Ataluren is thought to act by interfering with the ribosomal translational machinery so that premature nonsense stop codons in the messenger ribonucleic acid (mRNA) are read through by the translational machinery. This results in the translation of the entire mRNA and consequently production of a full-length protein product.¹,²

There are currently no curative treatments available for Duchenne muscular dystrophy. Management is based on prevention and management of complications and includes the use of prednisone/prednisolone (or deflazacort), which are the only treatments that have been demonstrated to temporarily reduce the decline in motor function in patients with Duchenne muscular dystrophy.¹

Evidence of efficacy comes from study PTC124-GD-007-DMD/ Study 007 (referred to hereafter as study 007), a randomised, double-blind, placebo-controlled phase Ib study conducted in males aged at least five years old with Duchenne muscular dystrophy resulting from documented nonsense mutation in the dystrophin gene. Eligible patients had onset of dystrophinopathy symptoms by nine years of age, an elevated serum creatine kinase and
difficulty ambulating but able to walk at least 75 metres (m) unassisted during the 6-minute walk test (6MWT). Stable use of concomitant glucocorticoids was permitted.\(^1,^3,^4\)

Patients were randomised equally to oral treatment with ataluren 40mg/kg/day (administered in three divided doses: 10mg/kg, 10mg/kg, 20mg/kg) (licensed dose); ataluren 80mg/kg/day (as three doses: 20mg/kg, 20mg/kg, 40mg/kg); or placebo for 48 weeks, stratified by age (<9 or ≥9 years), use of glucocorticoids (yes or no), and baseline 6-minute walking distance (6MWD) (≥350m or <350m).\(^3\)

The primary outcome was change from baseline to week 48 in the 6MWD analysed in the intent-to-treat (ITT) population, which included all randomised patients with a valid 6MWT available at baseline and at least one post-baseline visit. A corrected ITT (cITT) population was defined post hoc. This took account of two patients (in the placebo and ataluren 80mg/kg/day groups) with lower limb injuries before the baseline test, which resulted in the baseline 6MWDs being much lower than the screening and week six values. For these two patients, the baseline 6MWD values were replaced by the screening value in the cITT analysis. Results of the primary endpoint in the ITT and cITT analysis for placebo and ataluren 40mg/kg/day (licensed dose) are included in table 1 below.\(^3,^4\)

Table 1: results of primary endpoint in study 007 \(^1,^4\)

<table>
<thead>
<tr>
<th>ITT analysis</th>
<th>Placebo (n=57)</th>
<th>Ataluren 40mg/kg/day (n=57)</th>
<th>Absolute difference</th>
<th>Difference (MMRM analysis) (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline 6MWD</td>
<td>360m</td>
<td>350m</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Mean change in 6MWD at week 48</td>
<td>-42.6m</td>
<td>-12.9m</td>
<td>29.7m</td>
<td>26.4m (-4.2 to 57.1)</td>
<td>p=0.2539 (adjusted, rank-transformed)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>cITT analysis</th>
<th>Placebo (n=57)</th>
<th>Ataluren 40mg/kg/day (n=57)</th>
<th>Absolute difference</th>
<th>Difference (MMRM analysis) (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline 6MWD</td>
<td>361m</td>
<td>350m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change in 6MWD at week 48</td>
<td>-44.1m</td>
<td>-12.8m</td>
<td>31.3m</td>
<td>31.7m (5.1 to 58.3)</td>
<td>p=0.0197 (nominal, untransformed), p=0.0356 (adjusted, untransformed)</td>
</tr>
</tbody>
</table>

MMRM=mixed-model repeated-measures; ITT=intent-to-treat; cITT=corrected ITT; CI=confidence interval; 6MWD=6-minute walking distance

A post hoc analysis was undertaken in the subgroup of patients who were considered in the decline phase of their disease. This subgroup included patients aged over seven years, treated with corticosteroids, with a baseline 6MWD ≥150m and who had demonstrated a value ≤80% of their predicted 6MWD (ie signifying a decline in walking ability). These criteria were based on the natural history of the disease observed in patients in the placebo arm of the study. The number of patients in the placebo subgroup was 31 and in the ataluren subgroup was 32. The mean change in 6MWD from baseline to week 48 was -62.2m for placebo and -12.3m for ataluren 40mg/kg/day; observed difference 49.9m, p=0.0096 (nominal, untransformed).\(^1\)

Secondary endpoints included time function tests (ascend four stairs, descend four stairs, 10m run/walk, and supine to stand). There were numerical differences in favour of ataluren for all
except supine to stand, where results for ataluren were similar to placebo. A hand-held myometer was used to record upper and lower extremity using standardised procedures. Decline in muscle strength at 48 weeks was less for patients in the ataluren 40mg/kg/day group compared to placebo although differences were lower than the clinically meaningful difference of 2.0lbs.\(^3\)

Accidental falls were recorded daily in patient/care-giver-reported diaries. In the placebo group, mean falls/day was 0.54 at baseline and 0.72 at week 48, and in the ataluren 40mg/kg/day group, was 0.27 and 0.23 respectively. The relative ratio for ataluren 40mg/kg/day versus placebo was 0.38, 95% confidence interval (CI): 0.16 to 0.96. There was a positive trend in favour of ataluren 40mg/kg/day for patient-reported wheelchair use. There was an increase in mean percentage of days of wheelchair use from baseline to week 48 of 11.5% (95% CI: 4.4 to 18.5) for placebo versus 4.0% (95% CI: -2.8 to 10.7) for ataluren 40mg/kg/day.\(^1,3\)

Quality of life was measured using the Pediatric quality of life inventory (PedsQL). The difference in PedsQL physical functioning score for ataluren 40mg/kg/day versus placebo at week 48 was 3.4. In the decline phase subgroup (post hoc analysis) the difference in physical functioning score for ataluren 40mg/kg/day versus placebo at week 48 was 6.1.\(^1,3\)

Study PTC124-GD-020-DMD/ Study 020 (study 020) is being conducted in male patients aged 7 to 16 years with Duchenne muscular dystrophy due to nonsense mutation in the dystrophin gene, and receiving a stable dose of corticosteroids (for at least six months). In addition, patients were to have a 6MWD at screening ≥150m and ≤80% predicted 6MWD (for age and height). A total of 230 patients were randomised (stratified by age, duration of corticosteroid use and baseline 6MWD) to placebo (n=115) or ataluren 40mg/kg (n=115). The company are to report results of this study to the EMA within the terms of the conditional marketing authorisation, and they are currently being analysed for this purpose. Topline results became available after the company submitted to SMC and on request these have been provided to SMC. In the ITT population (n=228) the difference in mean change from baseline to week 48 in the 6MWD for ataluren versus placebo was 15m (p=0.213) and in a pre-specified subgroup (patients with 6MWD of 300m to 400m at baseline, n=99) the difference was 47m (p=0.007).\(^1,4,6\)

Other data were also assessed but remain commercially confidential.*

### Summary of evidence on comparative safety

Treatment emergent adverse events were generally classed as mild or moderate. Those occurring in ≥20% of patients in either group (in the placebo and ataluren 40mg/kg/day groups respectively) included: vomiting (39% versus 56%), diarrhoea (25% versus 19%), pyrexia (21% versus 25%), nasopharyngitis (23% versus 23%) and headache (25% versus 39%).\(^4\)

No patient discontinued treatment or withdrew from the study due to an adverse event. Serious adverse events occurred in a similar proportion of patients: 5.3% (3/57) in the placebo group versus 3.5% (2/57) patients in the ataluren 40mg/kg/day group. No serious adverse events were considered related to ataluren treatment. Ten patients treated with ataluren (and one placebo-treated patient) had grade 1 elevations in gamma-glutamyl transferase (GGT) or total bilirubin. Cholesterol and triglycerides increased in patients receiving ataluren (and less so in placebo-treated patients) from mean baseline values which were in the upper range of normal.\(^3,4\)
Differences in incidences of adverse events were noted depending on the age of the patient. Younger patients (aged 5 to 6 years) reported vomiting, pyrexia, abdominal pain, influenza and viral gastroenteritis more frequently than older patients. Conversely, headache, diarrhoea, upper abdominal pain, nausea, falls, procedural pain, pain in extremity, back pain, rash, flatulence, disease progression, oropharyngeal pain and dizziness occurred more frequently in older than younger patients.¹

### Summary of clinical effectiveness issues

In patients with Duchenne muscular dystrophy, symptoms of muscle weakness occur from around three years of age, and assisted ventilation is usually required in late teens. Prognosis is poor, with respiratory complications or heart failure causing death in the second to fourth decades of life.⁴ There are no curative treatments for Duchenne muscular dystrophy. Prednisolone (which temporarily reduces the decline in motor function) is offered to patients aged at least four years, providing the adverse effect profile is acceptable to the patient, family and physician.⁷

Ataluren is a first in class oral treatment for ambulatory patients aged five years and older with Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene.¹ It has conditional marketing authorisation from the EMA. Ataluren meets SMC ultra-orphan criteria and has been designated an orphan medicine by the EMA.

The difference in mean change in 6MWD from baseline to week 48 was statistically significant, in favour of ataluren compared with placebo in the post hoc cITT analysis of study 007, in which approximately 71% of patients were receiving concurrent corticosteroids. The mean difference was 32m, which is higher than the value of 30m considered to be clinically meaningful.¹ At the time of the study design there was no accepted primary endpoint for the treatment of Duchenne muscular dystrophy. During the study, the standard deviation increased over visits and was greater than 50m, the value used to estimate sample size, resulting in the study being under-powered.³

Overall, the EMA considered that the results of the secondary endpoints did not support the primary endpoint. There were trends in favour of ataluren for three of the time function tests (ascend four stairs, descend four stairs, 10m run/walk) and no difference versus placebo for the supine to standing test. There was little decline in muscle strength, which although severely affected in ambulatory patients, deteriorates at a much slower rate than muscle function and is less sensitive to change in disease status (compared to time function tests). The accidental fall analysis was limited by differences in baseline rates between the ataluren and placebo groups. Wheelchair data captured the day in which wheelchair was used only, and not the total duration of use of a wheelchair, nor did it consider variability in performance and the actual need for use of a wheelchair.¹³

By delaying ambulatory decline, patients may remain self-sufficient for longer. As the study duration was relatively short (48 weeks), other potential benefits (eg prevention or delay of onset and reduced severity of scoliosis and the need for major surgery) were not measured. Only ambulant patients were enrolled in study 007 (able to walk at least 75m unassisted during a 6MWT) and the summary of product characteristics notes that efficacy has not been demonstrated in non-ambulatory patients.³⁸ The decision to discontinue treatment with ataluren
when patients are no longer ambulant, will require careful consideration and discussion between the consultant, patient and family. This has been noted by clinical experts consulted by SMC.

The post hoc subgroup analysis in patients considered to be in decline phase of their disease was considered by the EMA to be exploratory. In this analysis, the difference in mean change in 6MWD from baseline to week 48 was 50m, in favour of ataluren. However, the EMA, when granting conditional marketing authorisation, considered that restricting use to patients in the decline phase was not scientifically plausible, given its effect on dystrophin production and likely benefit in patients with milder disease. Top line results from study 020, being conducted in the decline phase population, are available and the analysis of these data is to be reported to the EMA as part of the conditional marketing authorisation.¹

Ataluren appears to be well tolerated. As the majority of patients are likely to receive concurrent corticosteroids, the careful management of adverse events (eg elevation of serum lipids and blood pressure) will be important. ⁴ Ataluren is administered three times daily, orally by mixing the granules to a suspension in liquid or in semi-solid food.⁸

Clinical experts consulted by SMC considered that ataluren was a therapeutic advancement in terms of its mode of action and being a first in class treatment. They considered that ataluren would be used in addition to current treatment strategies, including corticosteroids.

### Summary of patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of ataluren, as an ultra orphan medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- DMD is a devastating, life limiting, childhood condition that has a significant physical and psychological impact on the patients and their families. Patients generally lose ambulation by 8-10 years, requiring permanent wheelchair use, and the current life expectancy is around 25 years.

- Ataluren is the first treatment that provides an opportunity to address the underlying cause of DMD and the benefits are additional to corticosteroids which are the current standard of care. While corticosteroids have improved survival and quality of life in DMD they are associated with a severe adverse effect profile which limits their use in practice.

- The potential to delay the loss of ambulation until after puberty with the preservation of independence also supports maintenance of respiratory and cardiac function and reduces the risk of scoliosis.

- Any extension to life or a longer period of that life that is spent ambulant and in the best possible health, is a significant proportion of the total life expectancy for boys with DMD.

- Access to ataluren will give patients and their families the hope that muscle function may be preserved until further treatment options are available
Summary of ultra-orphan decision making framework

Ataluren has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines. Relevant factors under each of the criteria are summarised below:

**Nature of the condition**
Duchenne muscular dystrophy (DMD) is a severe, progressive and rare genetic muscle wasting disease characterised by a rapid decline in physical functioning starting in childhood with subsequent respiratory and cardiac failure, leading to death in early adulthood. The psychological and psychosocial impact on boys is highly significant as they lose their independence and recognise that they cannot keep up with their peers. This can lead to behavioural or mental health issues making it difficult to maintain friendships, with the potential for social isolation.

Patients generally lose ambulation by 8-10 years, requiring permanent wheelchair use and consequently they may not be able to visit family and friends at their homes; it also becomes more difficult to travel and they may have to change school. As muscle function is lost in the arms, the boys are no longer able to self care. The progressive loss of muscle function leads to scoliosis and the need for surgery. Respiratory insufficiency and cardiac complications develop in time, and cardiac or respiratory failure are the most common causes of death for individuals with DMD.

**Impact of new technology**
In the trial setting, ataluren has been shown to slow the decline in six-minute walk distance in boys with DMD, relative to placebo. This is expected to result in a delay to wheelchair dependency; delayed time to respiratory complications; and an extension to life. The benefits of ataluren are additive to the effects of corticosteroids.

If this benefit was sustained then patients may maintain ambulation through childhood into early adult life. This may reduce the risk of scoliosis and the need for spinal surgery.

PACE participants highlighted that patients receiving treatment in the trial setting have experienced a range of benefits not captured in the trial including reduced behavioural issues, increased endurance and benefits for other muscle functions. Patient reported outcomes indicate that baseline mobility has been maintained. Benefits have also been seen in the energy levels required to function alongside their peers, their lung function and upper body strength. Consequently, boys have been able to stay in full time education, continue to participate in sports and maintain their independence.

**Value for money**
The submitting company presented a cost-utility analysis which compared ataluren plus best supportive care (BSC) to BSC in the licensed indication. BSC consisted of corticosteroids, physical therapy, inpatient intervention, surgery or rehabilitation if required, dietetic advice and psychological support.

The company used a multi-state semi-Markov model to assess the cost-effectiveness of ataluren versus the comparator. In terms of model structure, patients entered the model in the ambulatory health state and could remain in the health state or transition to the non-ambulatory health state. Patients in the non-ambulatory health state can remain in the health state or
transition to the ‘non-ambulatory and ventilation assisted’ health state or the ‘non ambulatory and scoliosis health state’. Patients in the non-ambulatory, ‘non-ambulatory and ventilation assisted’, and the ‘non ambulatory and scoliosis’ health states were also able to transition to a ‘non-ambulatory and ventilation assistance plus scoliosis’ health state, or remain in their health state. Death was included in the economic model, and patients who were ambulatory could die from non-Duchenne muscular dystrophy causes. Patients who were in the non-ambulatory health states could die from Duchenne muscular dystrophy or other causes. The analysis assumed patients would be treated with ataluren until loss of ambulation.

The sources of the clinical data used in the economic model included study 007, which was used to extrapolate a mean time to loss of ambulation for BSC and ataluren. Published sources were used to estimate time to loss of ambulation curves, transition probabilities from the non-ambulatory health state to the ventilation assistance and/or scoliosis health states for the comparator, and the transition to the death health state for BSC. To estimate the transition to death for ataluren, a relative risk of death was applied to the BSC mortality estimate. The relative risk was also informed by the published literature and assumption, though this was considered a conservative estimate by the company. Adverse events were not included in the analysis.

Utility estimates were taken from published sources and were treatment specific for the non-ambulatory health states. The analysis also included a caregiver disutility of 0.22 which was applied to both arms of the analysis. When the treatment specific values and the carer disutilities were included in the model, the health state utilities ranged from 0.66 to -0.17 for ataluren, depending on the health state. The health state utilities for BSC ranged from 0.66 to -0.3 depending on the health state.

Medicines costs were included in the analysis, and the model did not include any monitoring or administration costs for ataluren. Costs associated with BSC such as disease management and surgery were included in the analysis.

The base case results indicated that the incremental cost effectiveness ratio (ICER) for ataluren versus BSC was £793,498. This result was based on an incremental cost of £4,831,213 and an incremental quality adjusted life year (QALY) gain of 6.089. It should be noted that the company’s base case results included an assumption that after 14 years the medicine acquisition cost of ataluren would reduce by 50% due to patent expiry and also included carer disutilities. These assumptions would not normally be considered as part of SMC’s base case and removing them resulted in an ICER of £974,256 on the basis of an incremental cost of £5,034,267 and a QALY gain of 5.167.

The ICER was most sensitive to reducing the cost discount rate up to 30 years to 0% (£1,270,389), increasing the outcome discount rate up to 30 years to 6% (£1,249,819), reducing the ambulatory patient utility by 20% (£1,147,031), reducing the time horizon to 20 years (£1,079,645), and including the incidence of scoliosis after puberty (£1,039,384). These results reflect SMC’s preferred base case assumptions (ie price reduction on patent expiry not assumed and carer disutilities excluded).

In relation to carer disutilities, an analysis was however presented to include this aspect and this was relevant for SMC to consider as sensitivity analysis given the ultra-orphan nature of the medicine. This reduced the ICER of £826,849.
A Patient Access Scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS a simple discount is offered on the cost of the medicine.

SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

The main weaknesses were

- The economic model draws mainly on published literature, as opposed to direct comparative data from study 007. For example, the published literature was used to generate outcomes such as time to loss of ambulation curves and transition probabilities to the non ambulatory ventilation assistance and/or scoliosis and death health states. In addition, the longer term efficacy of ataluren is influenced by the relationship that delaying loss of ambulation delays or prevents scoliosis, ventilation assistance or death. As the economic model estimated that ataluren delays loss of ambulation, these efficacy outcomes may be more favourable for ataluren versus BSC. However, time to scoliosis, ventilation assistance and death were not directly measured for ataluren and, therefore, improved longer term efficacy was based on assumption only. The company response indicated that published data were used in the analysis because of limitations with the available clinical data. These included the relatively short duration of the pivotal study and the fact that few patients in the pivotal study lost ambulation. The company also provided supporting references which suggested that delaying time to loss of ambulation would delay time to scoliosis and ventilation assistance. Initial SMC expert responses have commented that it is reasonable to suggest that delaying loss of ambulation may lead to improved longer term outcomes for patients.

- In order to model time to loss of ambulation, the company estimated a treatment effect based on study 007 data and then applied the treatment effect to published natural history data. The approach adopted by the company was reliant on a number of assumptions and combining different sources of data which increased the uncertainty in the analysis. The treatment effect was estimated through a linear extrapolation of data from weeks 24-48 of the pivotal study, and the analysis reported that ataluren would delay loss of ambulation by around 8.1 years compared with BSC. The linear extrapolation assumed that the efficacy of ataluren would remain constant over time and the relative effect versus placebo would also be maintained. To apply the treatment effect estimated from the linear extrapolation to published natural history data, the company assumed the placebo arm of the pivotal study was similar to the published study data. The company response indicated that, due to the short duration of study 007, the pivotal study alone was insufficient when modelling loss of ambulation and therefore additional data sources may have been required. The company also noted that the published natural history data were similar to the pivotal study as the mean time to loss of ambulation from the linear extrapolation was comparable to the median time to loss of ambulation from the published data. Assuming a constant treatment effect was considered a plausible assumption by the company given the mode of action of ataluren.

- The analysis included treatment specific utility values for the non-ambulatory health states which favoured ataluren versus BSC. The company has provided an analysis where the utility values for each health state are the same for both medicines which increased the ICER to £1,160,886 (without PAS).

- The economic analysis assumed that patients would be treated with ataluren until loss of
ambulation. However, SMC expert responses suggested that patients may remain on ataluren indefinitely. The company has provided a sensitivity analysis where treatment costs are included for 6 months after loss of ambulation. This analysis generated an ICER of £1,017,331 (without PAS).

- The baseline starting age of the cohort in the economic model was 8.5 but the licensed population is patients aged 5 or older. The company has provided a sensitivity analysis where the starting age of the cohort was 5 years old which increased the ICER to £1,112,150 (without PAS). However the company has commented that the analysis should be treated with caution and may not be appropriate due to difficulties in modelling the disease progression of 5-8.5 year olds.

Patient and clinician engagement
A Patient and Clinician Engagement (PACE) meeting was held for this submission. Participants at the PACE meeting indicated a range of potential impacts of the new technology for the patient and families/carers.

Impact beyond direct health benefits and on specialist services
Use of ataluren to maintain ambulation and slow disease progression has impacted dramatically on the quality of life for patients allowing them to maintain their independence for longer. There are a number of benefits including the ability to continue to self care, and being able to remain in mainstream education for longer.

The use of ataluren may also provide benefits for family and friends. A normal family life with routine outings and travel can be preserved. Parents can continue to work and need less time off work. The relationship between parents and their sons does not become one of a patient and carer. Parents can continue to provide a carer role for older family members.

PACE participants noted that the benefit of ataluren is part of a jigsaw with respect to future management of DMD. Other treatments are currently in development but trial participation will require boys to be ambulant. Access to ataluren in NHS Scotland will provide hope for DMD families that muscle function and ambulation will be maintained long enough for their boys to access the benefits of future therapy either in the trial setting or as new licensed treatment options.

It is noted that the company did provide an economic analysis which included wider benefits to carers. This reduced the ICER to £827k (without PAS).

Costs to NHS and Personal Social Services
The company reported that 6 patients would be eligible for treatment in year 1 rising to 7 patients in year 5. Market share was estimated as 90% in each year 1. Once market share and treatment discontinuation were taken into account, this resulted in 5 patients being treated with ataluren in year 1 rising to 6 patients in year 5.

SMC would wish to present the estimated budget impact of ataluren for NHS Scotland, but owing to commercial in confidence concerns raised by the submitting company, SMC is unable to publish this information.

The Committee considered the benefits of ataluren in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the
criterion for the absence of other treatments of proven benefit was satisfied. In addition, as ataluren is an ultra-orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee was unable to accept ataluren for use in NHS Scotland.

*Other data were also assessed but remain commercially confidential.*

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**Summary of patient and public involvement**

The following information reflects the views of the specified Patient Groups.

- Submissions were received from Action Duchenne, Muscular Dystrophy UK (MDUK) and Harrison’s Fund, which are all registered charities.

- Both MDUK and Action Duchenne have received pharmaceutical company funding in the past two years, with both having received funding from the submitting company. Harrison’s Fund has not received any pharmaceutical company funding in the past two years.

- Duchenne muscular dystrophy (DMD) is a severe muscle-wasting disease. Average life expectancy is in the late 20s although many patients die younger due to the respiratory or cardiac complications associated with the disease. The complexities and costs of care increase as children age and lose the ability to walk. DMD places a heavy burden on families. In the UK, nearly half of caregivers reduced their working hours or stopped working completely owing to their relative’s condition.

- The current treatments on the NHS in Scotland focus on the management of symptoms, rather than addressing their underlying genetic cause.

- Ataluren should be considered a step change in the management of DMD as it is the only treatment available which addresses the underlying cause. It may slow the loss of ambulation which is associated with a faster progression of the disease, the later stages of which are frightening and absolutely devastating. A delay in any of the devastating consequences of the disease, no matter how short, is important.

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**Additional information: guidelines and protocols**

The Scottish Muscle Network published a multidisciplinary care pathway in 2009. It is recommended that the decision to start glucocorticoid treatment should be made by a physician experienced in management of Duchenne muscular dystrophy, after a full discussion with the affected child and the parents. The arrangements for long-term follow up should be made at a clinic/centre where medical and physiotherapy facilities for monitoring of disease activity and glucocorticoid therapy are available. In view of experience and familiarity within the UK, prednisolone 0.75mg/kg/day (maximum dose 40mg/day) is recommended first-line. Alternatively in prednisolone treated boys who have excessive weight gain which is unresponsive to dietary/exercise/dose adjustments, deflazacort can be considered (0.75mg prednisolone=0.9mg deflazacort). Glucocorticoid therapy is generally not recommended in those aged up to three
years. From age four years, glucocorticoid therapy should be offered providing the adverse effect profile is acceptable to the patient, family and physician. Glucocorticoid treatment may be discontinued if:

- there is no improvement/stabilisation over the first six months of treatment
- the presence of side effects is unacceptable to the child/parents/physician
- there is a loss of ambulation. In this situation, the risks and side effects of ongoing treatment may outweigh the potential benefits. However, in view of the possible benefit to arm and respiratory function, this policy needs to be kept under review and under discussion with families.

The guideline predates the licensing of ataluren for Duchenne muscular dystrophy.

**Additional information: comparators**

Ataluren would be prescribed in addition to best supportive care which includes corticosteroids.

**Cost of relevant comparators**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per year (£)</th>
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<tbody>
<tr>
<td>Ataluren</td>
<td>40mg/kg orally daily given as three doses (10mg/kg, 10mg/kg, 20mg/kg)</td>
<td>154,030 to 739,344</td>
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</tbody>
</table>

Cost of ataluren is from the company’s submission. Cost is based on weight range 16kg to 70kg (from pivotal study) and the sachet use recommended in the summary of product characteristics. Costs do not take any patient access schemes into consideration.

**Additional information: budget impact**

The company reported that 6 patients would be eligible for treatment in year 1, rising to 7 patients in year 5. Market share was estimated as 90% in each year. Once market share and treatment discontinuation were taken into account, this resulted in 5 patients being treated with ataluren in year 1, rising to 6 patients in year 5.

SMC would wish to present the estimated budget impact of ataluren for NHS Scotland but, owing to commercial in confidence concerns raised by the submitting company, SMC is unable to publish this information.

*Other data were also assessed but remain commercially confidential.*
References

The undernoted references were supplied with the submission.


2. Bladen C SD, Monges S et al.. The TREAT-NMD DMD global database: analysis of more than 7,000 Duchenne muscular dystrophy mutations. Human Mutation. 2015;36:395-402.


5. Commercial in Confidence*

6. Commercial in Confidence*


This assessment is based on data submitted by the applicant company up to and including 08 January 2016.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on
the basis of a patient access scheme that has been considered feasible by PASAG, a set of
guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics
Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after
careful consideration and evaluation of the available evidence. It is provided to inform the
considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in
determining medicines for local use or local formulary inclusion. This advice does not override
the individual responsibility of health professionals to make decisions in the exercise of their
clinical judgement in the circumstances of the individual patient, in consultation with the patient
and/or guardian or carer.