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SMC2188

inotersen 284mg solution for injection in pre-filled syringe (Tegsedi®)

Akcea Therapeutics UK Ltd

5 July 2019

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 NHSScotland. The advice is summarised as follows:

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

inotersen (Tegsedi®) is accepted for use within NHSScotland.

Indication under review: for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR).

In a phase II/III study of adults with hATTR and polyneuropathy, inotersen was associated with significantly less worsening compared with placebo, measured by the change in modified neuropathy impairment score +7 (mNIS+7) and in Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) questionnaire from baseline to 66 weeks.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of inotersen. This advice is contingent upon the continuing availability of the PAS in NHSScotland or a list price that is equivalent or lower.

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

Chairman
Scottish Medicines Consortium

Indication

For the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR).[1]

Dosing Information

The recommended dose is inotersen 284mg by subcutaneous injection administered once every week. For consistency of dosing, patients should be instructed to receive the injection on the same day every week. Sites for injection include the abdomen, upper thigh region, or outer area of the upper arm. It is important to rotate sites for injection.

Inotersen is associated with reductions in platelet count, which may result in thrombocytopaenia. Dosing should be adjusted according to laboratory values; see the Summary of Product Characteristics (SPC) for further detail.

Treatment should be initiated by and remain under the supervision of a physician experienced in the treatment of patients with hereditary transthyretin amyloidosis.[1]

Product availability date

August 2019.
Inotersen was been designated an orphan medicine for the treatment of ATTR amyloidosis by the European Medicines Agency.
Inotersen meets SMC ultra-orphan criteria.

Background

Inotersen is a 2'-O-2-methoxyethyl (2'-MOE) phosphorothioate antisense oligonucleotide inhibitor of human transthyretin (TTR) production. By binding to TTR messenger ribonucleic acid (mRNA), inotersen degrades mutated and normal TTR mRNA, preventing the synthesis of TTR protein in the liver and significantly reducing mutant and normal TTR protein entering the circulation.[1] Inotersen has received marketing authorisation for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR.[1, 2]

Inotersen for use in this indication has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines.

Nature of condition

Hereditary transthyretin amyloidosis (hATTR) is a rare, progressive and fatal disease caused by mutations in the transthyretin (TTR gene). This leads to production of abnormal TTR protein in the liver which accumulates as deposits in the tissues of the body (amyloidosis).[2] The resulting amyloidosis, can alter the structure and impair the function of the affected tissues, leading to a range of symptoms involving one or more body system, including polyneuropathy and cardiomyopathy. Treatment options are limited and are largely restricted to symptom relief and supportive measures. The prognosis varies depending on the genotype and presence of any cardiac amyloidosis but survival estimates have been reported as 3 to 15 years from the onset of symptoms.[2] Orthotopic liver transplant is an option for a small number of suitable patients. Licensed treatment options are TTR tetramer stabilisers (such as tafamidis) which has not been recommended for use by SMC due to a non-submission and unlicensed diflunisal. In June 2019, SMC issued advice that patisiran is accepted for use by SMC for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR. In view of the timelines, patisiran is not considered a comparator in this assessment of inotersen.

Inotersen is the first antisense oligonucleotide inhibitor of human TTR production to be granted marketing authorisation in the UK.[1] Inotersen meets SMC ultra-orphan criteria. Clinical experts consulted by SMC considered that inotersen fills an unmet need in this therapeutic area, due to the lack of alternative treatment options at present.

A patient and clinician engagement (PACE) meeting was held to consider the added value of inotersen in the context of treatments currently available in NHSScotland. At the PACE meeting, hATTR was described as a devastating, fatal disease. Polyneuropathy associated with hATTR is a chronic, progressive and painful condition. Patients usually experience multiple symptoms, including decline in balance and mobility, neuropathic pain, weight loss, muscle wasting, reduced grip strength, alternating diarrhoea and constipation, sexual dysfunction, vision problems and symptoms associated with heart failure, such as fatigue and ankle oedema. These can substantially impact the patient's quality of life and dignity. The patient may have difficulty maintaining independent living or employment, leading to financial problems, and have problems participating in family life and society. In addition to the devastating effect on the patient, this condition can put a huge strain on the patient's family or carer as they care for the patient with increasingly worsening symptoms and worry about future progress of the disease, which is ultimately fatal. They may experience issues maintaining employment or feel stressed dealing with family commitments while attending to the increasing care needs of the patient. As the condition is hereditary it is possible that more than one family member is affected, which can add to the burden of the patient and carer. It might be that the carer also has hATTR. The hereditary aspect may compound the

marked psychological impact of the disease as the patient may have observed severe symptoms in an older relative or may worry about their children developing the condition.

It was also noted that there are currently no medicines which alter the course of hATTR polyneuropathy. Treatments are mainly symptomatic, for example pain management, mobility and nutritional support and reducing the effects on other organs. Some patients may be prescribed off-label medicines, for example diflunisal, and a small number of patients have liver transplants.

Impact of new technology

Summary of evidence on comparative efficacy

The key evidence to support the use of inotersen in patients with hATTR and polyneuropathy comes from one double-blind, randomised, phase II/III study (NEURO-TTR). Eligible patients were aged 18 to 82 years old and diagnosed with stage 1 (patient is ambulatory) or stage 2 (patient is ambulatory with assistance) hATTR with polyneuropathy. They had a Neuropathy Impairment Score (NIS) of ≥10 to ≤130 (range 0 to 244, with higher scores indicating more impairment), TTR mutation by genotyping, documented amyloid deposit on biopsy and a Karnofsky performance status score >50. In addition, patients with stage 1 polyneuropathy enrolled from Germany, Portugal and Argentina must also have failed to respond to, be intolerant of or not be eligible for tafamidis.[2, 3]

Patients were randomised in a ratio of 2:1 to receive inotersen 284mg (n=112) or placebo (n=60) by subcutaneous injection once weekly for 64 weeks, following three injections in the first week to achieve steady state medicine levels. Randomisation was stratified by TTR mutation (Val30Met versus non-Val30Met), stage of disease (stage 1 versus stage 2) and previous treatment with either tafamidis or diflunisal (yes versus no). Of the total 67 doses, 13 were administered at clinical visits, while the remainder could be administered at home by the patient, carer or health care professional. All patients received vitamin A supplementation (approximately 3000IU daily). Patients were not allowed to receive tafamidis or diflunisal during the study period.[2, 3]

The study had two primary outcomes:

- change from baseline to week 66 in modified neuropathy impairment score +7 (mNIS+7; maximum of 346) which consists of two composite scores: the NIS composite score (range 0 to 244) and the modified +7 composite score (maximum of 102.3). The NIS composite score includes four components (cranial nerves, muscle weakness, reflexes and sensation in fingers and toes). The modified +7 composite score includes four components (heart rate deep breathing, nerve conduction tests, touch-pressure sensation and heat-pain sensation).[2, 3] The minimum clinically

significant difference in mNIS+7 is considered to be 2 points.

- change from baseline to week 66 in total score of Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) questionnaire which comprises 35 questions (total score ranges from -4 to 136, with higher scores indicating poorer quality of life). There are five subdomains including physical functioning/large fiber neuropathy, activities of daily living, symptoms, small fiber neuropathy and autonomic neuropathy.[3]

The primary analysis was performed using mixed effects models with repeated measures (MMRM) in the full analysis set which included all randomised patients who had received at least one dose of study medicine and had at least one post-baseline efficacy assessment of mNIS+7 or Norfolk QOL-DN. A number of sensitivity analyses assessed different methods of handling missing data, some in the safety set population which included all patients who received at least one dose of study medicine. Since a higher proportion of inotersen than placebo patients discontinued treatment early, the European Medicine Agency (EMA) considered one of the sensitivity analyses (multiple imputation assuming jump to reference in the safety set) to be more relevant than the primary analysis because it included results for discontinuing patients using placebo-based imputation.[2] Results for both analyses statistically significantly favoured inotersen. At week 66, the mean mNIS+7 score increased from baseline significantly less in the inotersen group than in the placebo group, indicating less neurological worsening. There was little change from baseline to week 66 in quality of life (measured by the Norfolk QOL-DN questionnaire) in the inotersen group compared with an increase in the placebo group (indicating a worsening). Details are presented in table 1 below. [1-3]

Table 1: Results for the primary outcomes of the NEURO-TTR study based on the primary MMRM analysis in the full analysis set and key sensitivity analysis in the safety set[1-3]

	mNIS+7		**Norfolk QOL-DN**	
	Inotersen (n=85)	**Placebo (n=52)**	**Inotersen (n=85)**	**Placebo (n=52)**
Primary analysis using MMRM in full analysis set				
Baseline	79.2	74.8	48.2	48.7
LSM change	5.80	25.53	0.99	12.67
Difference (95% CI) versus placebo, p-value	-19.73 (-26.43 to -13.03) p<0.001		-11.68 (-18.29 to -5.06) p<0.001	

Key sensitivity analysis, using multiple imputation assuming jump to reference, in safety set				
	Inotersen (n=112)	**Placebo (n=60)**	**Inotersen (n=111)**	**Placebo (n=59)**
LSM change	10.54	25.43	4.38	12.94
Difference (95% CI) versus placebo, p-value	-14.89 (-22.55 to -7.22) p<0.001		-8.56 (-15.42 to -1.71) p=0.015	

mNIS+7= modified neuropathy impairment score +7; Norfolk QOL-DN= Norfolk Quality of Life-Diabetic Neuropathy questionnaire; LSM=least square mean; CI=confidence interval; MMRM= mixed effects models with repeated measures

Results for the components of mNIS+7 and domains of Norfolk QoL-DN composite scores were consistent with the primary outcome analysis, showing benefit in motor, sensory and autonomic neuropathies. In addition, subgroup analyses indicated a consistent treatment effect for both primary outcomes across all subgroups including genotype (V30M versus non-V30M), disease stage (stage 1 versus stage 2), previous treatment with tafamidis or diflunisal (yes versus no), cardiac subpopulation, age (<65 versus ≥65), gender, race (white versus non-white) and region (North America, Europe, South America and Australasia).

Secondary outcomes included and results are presented in table 2 below:

- change from baseline in the Norfolk QoL-DN questionnaire symptoms domain score in stage 1 patients
- change from baseline in the Norfolk QoL-DN questionnaire physical functioning/large fibre neuropathy domain score in stage 2 patients
- change from baseline in the modified body mass index (mBMI)
- change from baseline in the body mass index (BMI)
- change from baseline in the NIS
- change from baseline in the mNIS+7
- global longitudinal strain (GLS) by echocardiogram (ECHO) in the ECHO subgroup and in the Cardiomyopathy-ECHO (CM-ECHO) Set

Table 2: Results for secondary outcomes of NEURO-TTR at week 66 based on the primary (MMRM) analysis and the key sensitivity analysis 6[2, 3]

	Inotersen	Placebo	Difference (95% CI)	
			Primary MMRM	Key sensitivity analysis, using multiple imputation assuming jump to reference, in safety set
Change from baseline in Norfolk QoL-DN symptoms score Stage 1 patients	(n=55) -1.42	(n=33) 1.11	-2.53 (-4.49 to -0.57)	-1.75 (-3.46 to -0.04)
Change from baseline in Norfolk QoL-DN physical functioning/large fiber neuropathy score in Stage 2 patients	(n=29) 0.78	(n=19) 9.04	-8.25 (-14.71 to -1.80)	-6.34 (-12.07 to -0.62)
Change from baseline in BMI	(n=82) -0.30	(n=49) -0.80	0.5 (0.00 to 1.01)	0.33 (-0.12 to 0.78)
Change from baseline in NIS composite score	(n=85) 5.40	(n=52) 18.65	-13.25 (-17.65 to -8.85)	-9.54 (-14.55 to -4.52)
Change from baseline in NIS+7	(n=85) 5.90	(n=52) 20.39	-14.50 (-19.03 to -9.96)	-10.65 (-15.79 to -5.52)

NIS+7= neuropathy impairment score +7; Norfolk QOL-DN= Norfolk Quality of Life-Diabetic Neuropathy questionnaire; CI=confidence interval; BMI=body mass index; MMRM= mixed effects models with repeated measures; NIS=neuropathy impairment score

There were no significant differences between inotersen (n=50) and placebo (n=25) in global longitudinal strain in the pre-specified cardiomyopathy echocardiogram (CM-ECHO) subpopulation. In addition, there were no significant differences between inotersen and placebo in other echocardiographic parameters of left ventricular size and function, including interventricular septum thickness, posterior wall thickness and left ventricular mass.[3]

Patients who satisfactorily completed the NEURO-TTR study were eligible to enter the open-label extension study and receive inotersen 284mg by subcutaneous injection once weekly

for up to 5 years. The study is ongoing, however available data from an interim analysis suggest the continued benefit of inotersen on mNIS+7 and Norfolk QoL-DN which were assessed as secondary outcomes.[2, 4]

Summary of evidence on comparative safety

During the 15 month placebo-controlled period of NEURO-TTR, an adverse event was reported by 99% (111/112) of inotersen patients and 100% (60/60) of placebo patients and at least one event was considered to be treatment-related in 78% and 38% of patients respectively. Serious adverse events were reported in 32% of inotersen and 22% of placebo patients and these were considered treatment-related in 7.1% and 1.7% of patients respectively. Discontinuation due to adverse events were reported in 14% of inotersen and 3.3% of placebo patients.[2, 3]

The most commonly reported adverse events in the inotersen and placebo groups respectively were: injection site erythema (31% versus 0%), nausea (31% versus 12%), fatigue (25% versus 20%), diarrhoea (24% versus 20%), headache (23% versus 12%), injection site pain (21% vs. 6.7%), pyrexia (20% versus 8.3%), , urinary tract infection (19% versus 20%), peripheral oedema (19% versus 10%), chills (18% versus 3.3%), myalgia (15% versus 10%), vomiting (15% versus 5.0%), thrombocytopaenia (13% versus 1.7%), constipation (13% versus 10%), anaemia (13% versus 3.3%), injection site pruritus (12% versus 0%), dizziness (11% versus 12%) and platelet count decreased (11% versus 0%).[2, 3]

Inotersen has been associated with reductions in platelet count which may result in thrombocytopaenia. The summary of product characteristics (SPC) recommends platelet monitoring every 2 weeks during treatment and for 8 weeks after discontinuation. It also reports the degree of platelet count reductions in NEURO-TTR as below normal (140 x 10^9/L) in 54% of inotersen and 13% of placebo patients; as below 100 x 10^9/L in 23% and 2% of the patients respectively and as a confirmed platelet count of < 75 x 10^9/L in 11% of inotersen patients. Three (3%) inotersen-treated patients developed platelet counts < 25 x 10^9/L; one of these patients experienced a fatal intracranial haemorrhage. This death occurred before patients had regular platelet monitoring.[1, 3]

Glomerulonephritis was reported in three patients in the inotersen group and decline in renal function has been reported in some patients without signs of glomerulonephritis. Renal abnormalities are an established class effect of antisense oligonucleotides. The SPC recommends that urine protein to creatinine ratio and estimated glomerular filtration rate are monitored at least every 3 months and for 8 weeks after stopping treatment.[1, 3]

Inotersen is expected to reduce plasma vitamin A levels due to its mechanism of action. The SPC recommends that patients receiving inotersen should take oral supplementation of

approximately 3,000 IU daily of vitamin A to reduce the potential risk of ocular toxicity due to vitamin A deficiency.[1]

Summary of clinical effectiveness issues

In the key NEURO-TTR study in patients with hATTR amyloidosis and polyneuropathy, symptoms of neuropathy worsened to a lesser extent in the inotersen group compared with the placebo group, measured by the primary outcome mNIS+7. The minimum clinically important difference in mNIS+7 was considered to be 2 points and the difference between inotersen and placebo exceeded this. Additional training and duplicate assessments were carried out to standardise the efficacy assessment and reduce variability. There was also less worsening of quality of life (as measured by the Norfolk QOL-DN questionnaire) in the inotersen group compared with the placebo group. The results of both primary outcomes were statistically significant and clinically relevant and were supported by all secondary outcomes. The results indicate that the overall effect of inotersen in treated patients was to slow the progression of neuropathy but not stop or reverse it. There was consistency of treatment effect across components of the primary outcomes and across the different pre-specified subgroups. These treatment benefits were demonstrated despite differences between groups in baseline characteristics, in terms of disease stage and mNIS+7 score, which suggested that patients in the inotersen group may have had more severe disease at the study entry compared with patients in the placebo group.[2, 3]

The EMA noted that the primary analysis, using MMRM, was not considered of primary importance because it assumed that missing data were at random when there was an imbalance of patients excluded from the full analysis set due to a higher discontinuation rate in the inotersen group. One of the sensitivity analyses (placebo-based multiple imputation assuming jump to reference) was considered more appropriate since it accounted for the effect of treatment discontinuation and did not exclude these patients from the analysis.[2] Results using this analysis have been reported in the SPC and the differences between the treatment groups for both primary outcomes remained statistically significant, as detailed in tables 1 and 2 above. The between group difference was slightly smaller using this analysis since it assumed that missing results would be similar to those for placebo and may underestimate any continued treatment effect on neuropathy after discontinuation.[1, 2]

Limited results from the open-label extension study suggest that the treatment effect of inotersen is maintained but long-term data are needed. The NEURO-TTR study included patients with stage 1 and 2 polyneuropathy only and therefore the licensed indication does not extend to patients with more severe disease (stage 3 who are wheelchair-bound or bedridden). The NEURO-TTR study was primarily designed to show efficacy on polyneuropathy but a substudy also assessed cardiac parameters in a cardiac subpopulation. However, there were no significant effects of inotersen on selected cardiac parameters and

the EMA concluded that the efficacy of inotersen in the treatment of cardiomyopathy in patients with hATTR had not been sufficiently demonstrated. The NEURO-TTR study excluded patients with NYHA class III or IV so the treatment effect in patients with significant symptoms of heart failure is unknown.[2, 3]

The safety profile of inotersen includes the risk of immune-mediated thrombocytopaenia, with its associated bleeding risk, and glomerulonephritis. These are to be managed by risk-minimisation measures including specific monitoring, dose reduction and stopping rules which are detailed in the SPC.[1, 2]

Clinical experts consulted by SMC considered that inotersen is a therapeutic advancement by slowing the progression of polyneuropathy.

At the PACE meeting, it was noted that inotersen, compared with placebo, stabilises progression of polyneuropathy and decline in quality of life. It minimises worsening of some symptoms, for example irreversible numbness due to nerve damage and can improve other symptoms, such as weight loss, fatigue and ankle oedema. It can halt the spread of some neuropathy symptoms (e.g. feeling of numbness) to new areas of the body. By keeping the patient in good health for longer it may help them to maintain dignity, quality of life, independent living, mobility and employment and allow them to participate to a greater extent in family life and society. It was also noted that as nerve damage is typically irreversible, the benefits of inotersen would be maximised by commencing treatment early in the course of the disease to provide the greatest impact on prevention of nerve damage and resulting symptoms.

Although there is a lack of long-term efficacy data beyond 18 months, PACE participants believe that, based on inotersen's pharmacology (i.e. reduction in levels of the protein [TTR] that produces the amyloidosis that damages nerves), it is reasonable to expect that benefits will continue beyond this into the longer term. They also consider that there is a theoretical potential for improvement in other aspects of hATTR with inotersen due to its pharmacology.

Patient and clinician engagement

A PACE meeting with patient group representatives and clinical specialists was held to consider the added value of inotersen as an ultra-orphan in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Polyneuropathy associated with hATTR is a chronic progressively deteriorating condition with a range of symptoms that markedly decrease the patient's quality of life and represent a huge burden of care for the patient's family or carers. Ultimately it can lead to a total loss of mobility and dignity. It has a substantial psychological impact on the patient and their family or carer, which is compounded by the hereditary nature of the disease and lack of effective treatment options.
- There are no medicines that alter the course of the disease and current management is mainly symptomatic, with limited efficacy as the disease progresses.
- Inotersen stabilises progression of neuropathy, with use early in the disease likely to maximise benefits. It may help the patient to maintain their quality of life, mobility, dignity and employment and allow them to participate to a greater extent in family life and society.
- Inotersen may also reduce the huge burden of care on the patient's family or carers and lessen the strain associated with maintaining employment and family commitments while caring for the patient.
- The availability of a disease-modifying medicine such as inotersen may lessen the psychological impact of the condition, especially if other family members are affected by hATTR.
- PACE participants advise that, based on inotersen's pharmacology, it is reasonable to expect that it would have long-term efficacy and benefits on other aspects of the condition, such as cardiomyopathy.
- Inotersen has a convenient once weekly administration schedule that allows patients to self-administer the medicine at home. Inotersen treatment may be associated with thrombocytopenia and renal adverse events, with regular monitoring for these required during treatment. While receiving inotersen the patient must have blood tests every two weeks.

Additional Patient and Carer Involvement

We received a patient group submission from the Amyloidosis Research Consortium UK, which is a registered charity. ARC UK has received 80% pharmaceutical company funding in the past two years, including from the submitting company. A representative from ARC UK

participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

Value for money

The company submitted a cost-utility analysis comparing inotersen to best supportive care (BSC) for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR-PN. SMC experts have noted that BSC is likely to be the appropriate comparator treatment.

A four state Markov model was submitted by the company which used a 41 year time horizon. Three health states were defined according to Coutinho staging, which measured disease severity i.e. stage 1 represented a health state where patients can walk without assistance, whilst stage 3 represented a health state where a patient requires a wheelchair or is bedridden and death was the fourth model state. Given that the pivotal study did not assess disease severity using Coutinho staging, the model relies on an assumption that Coutinho staging corresponds to the Norfolk QoL- DN. This assumption is supported inan ongoing NICE health technology assessment (HTA).

Disease progression in the model was captured using transition probabilities (based on Norfolk TQoL data from the pivotal study). The model linked TQoL to disease stages by estimating TQoL cut off scores, derived from the ongoing NICE HTA noted above. Transition probabilities for both treatment arms were modelled for three time points, week 0 to 35, week 35 to 66 and week 66 onwards. Efficacy from week 35 to 66 was used to estimate long term effectiveness in the model i.e. transition probabilities for week 35 to 66 were extrapolated over the modelled time horizon. Disease-related mortality was captured via the application of hazard ratios. Mortality data from the pivotal study were not mature and were not estimated according to Coutinho stages therefore data were taken from published literature which used polyneuropathy disability (PND) scores. The company assumed that PND scores corresponded to Coutinho stages, therefore modelled mortality hazard ratios were 2.01, 2.42 and 9.53 for stages 1, 2 and 3 respectively.

Medicine acquisition costs and monitoring costs were included in the analysis. Medicine costs for inotersen were estimated based on the proportion of patients remaining on treatment in the pivotal study and extrapolated using an exponential parametric curve. No administration costs were included for inotersen as treatment was assumed to be administered by either a patient or a carer. In the base case the company assumed that health state costs for patients on inotersen would be 43% lower in stage 1 and stage 2, compared to the BSC arm. The company assumed that patients would require one carer in Stage 1 and Stage 2 and two carers in stage 3 based on the results of a patient and caregiver impact survey. Adverse event costs were included.

Utility values used in the model were taken from published literature were based on quality of life data which weighted THAOS EQ-5D utility using a Brazilian valuation set. In order to generate UK-specific values, the company mapped the Brazilian values to UK values using local tariffs obtaining scores of 0.812, 0.205 and -0.094 for stage 1, 2 and 3 respectively. The model also applies treatment-specific utilities. For patients on inotersen the company applied a monthly utility of 0.0002 whilst for patients receiving BSC a utility decrement of 0.0038 was applied. Utility values were capped in order to ensure validity. Carer disutility was included in the base case and in addition, wider economic impact on patients was considered in sensitivity analysis. It should be noted that SMC guidance on the economic evaluation of ultra orphan medicines welcomes the inclusion of wider costs and benefits as sensitivity analysis.

A Patient Access Scheme (PAS) was proposed by the submitting company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Base case and key sensitivity analyses results are presented in Tables below.

Table 3: Base case results

Treatment	Incremental costs	Incremental quality adjusted life years (QALYs)	Incremental Cost effectiveness ratio (ICER)
BSC	-	-	-
Inotersen	£154,208	1.97	£78,088

Table 4: Scenario analyses results

	Scenario	ICER
1.	Inotersen impact on health state costs removed i.e. inotersen no longer assumed to result in reduced healthcare resource use for patients in stage 1 and stage 2	£137,184
2.	Inotersen impact on health state costs reduced to 25%	£102,826
3.	100% treatment compliance with inotersen	£102,261
4.	Log normal curve used to estimate treatment costs for inotersen	£101,478
5.	Treatment- specific utility adjustments removed	£80,838
6.	Carer disutility removed	£92,583
7.	Utility values based on THAOS registry data (Brazilian valuation set)	£89,182
8.	Waning of inotersen treatment efficacy (transition probabilities equivalent to BSC by year 5)	£114,880

9.	Waning of inotersen treatment efficacy (transition probabilities equivalent to BSC by year 10)	£96,956
10	Combined scenario analysis which included the following; -Health state cost differential for inotersen (for Stage 1 and Stage 2) reduced from 43% to 25% -Treatment specific utility adjustment removed -Carer disutility removed -Waning of treatment efficacy by year 10	£149,973
11	Societal perspective (carer disutility and economic impact on patient included)	£70,242

There were a number of limitations with the analysis which included the following;

- There is some uncertainty surrounding the long term effectiveness assumed for inotersen in the model. The company assumes that transition probabilities from week 35 to 66 within the pivotal study are likely to be reflective of longer term progression and therefore transition probabilities are extrapolated over the duration of the time horizon. While experts are supportive of the rationale for continuing effects of treatment, given the lack of data supporting this assumption, the health benefit associated with inotersen is subject to uncertainty. The company has provided scenario analyses reducing the efficacy of inotersen i.e. transition probabilities for inotersen gradually decreased after week 66 to the point that transitions were equivalent to BSC by year 5 and year 10. Results are presented in Table 4 above (scenario analysis 8 and 9).
- There was insufficient evidence provided to support the assumption that inotersen will result in 43% less healthcare resource use in Coutinho Stages 1 and 2 compared to patients on BSC. For completeness the company has provided sensitivity analysis which tests alternative assumptions. See scenario 1 and 2 presented in Table 4 above.
- There is some uncertainty surrounding the application of monthly utility adjustments to both treatment arms. Given Qol is already implicitly accounted for in the model via treatment efficacy, this has a 'double counting' effect, which may overestimate the Qol for patients receiving inotersen and underestimate the Qol for patients receiving BSC. Furthermore, given the lack of UK specific Qol data, there may be some uncertainty surrounding the health state utilities used in the model, which have been derived from a subset of Brazilian patients within the THAOS registry and adjusted for the UK population.
- The base case results are sensitive to the use of alternative parametric functions used to extrapolate the proportion of treatments over time. Based on the goodness of fit statistics and comment from the SMC statistician, the log logistic and log normal curves could be considered viable alternatives.

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

Impact beyond direct health benefits and on specialist services

Management of hATTR is a highly specialised service which is undertaken at The National Amyloidosis Centre in London. Treatment is initiated there and patients are regularly followed up every six months. The submitting company anticipates that inotersen treatment will be initiated at the national centre but that continuation of care will be through shared care arrangements with local clinicians in NHSScotland.

It was noted at the PACE meetng that by reducing the progression of symptoms of polyneuropathy and keeping the patient in good health for longer inotersen may allow the patients to maintain independent living, mobility and employment. Thereby lessening the burden of care on the patient's family or carers. Also, the availability of a disease-modifying medicine may reduce the psychological impact of the condition on the patient and their family or carer, especially if other family members are affected by hATTR.

Inotersen is administered by weekly subcutaneous injection allowing patients or carers the convenience of being trained to administer treatment at home, allowing them to maintain their independence. Inotersen treatment may be associated with thrombocytopenia (reduced platelet counts) and renal adverse events, with regular monitoring for these required during treatment. While receiving inotersen the patient must have blood tests every two weeks.

Costs to NHS and Personal Social Services

The company assumed there would be 6 patients eligible for treatment in year 1 rising to 9 in year 5 to which confidential estimates of market uptake were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

The submitting company did not estimate any costs outside the NHS in the budget impact calculations but did include wider impacts in the economic analysis above.

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

Conclusion

The Committee also considered the benefits of inotersen in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for a substantial improvement in quality of life was met. In addition, as inotersen is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted inotersen for use in NHSScotland.

Additional information: guidelines and protocols

No national guidelines relating to hATTR amyloidosis were identified.

Additional information: comparators

Supportive care.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Inotersen	**284mg once weekly by subcutaneous injection**	**308,100**

Costs from company submission. Costs do not take any patient access schemes into consideration.

References

1. Akcea Therapeutics. Inotersen solution for injection in pre-filled syringe (Tegsedi®). Summary of product characteristics. European Medicines Agency. Availabe at: www.ema.europa.eu. Last accessed: 07/03/2019.
2. European Medicines Agency. (EMA) European Public Assessment Report. inotersen (Tegsedi)®). 31/05/2018, EMEA H-C-004782. www.ema.europa.eu.
3. Benson MD, Waddington-Cruz M, Berk JL, Polydefkis M, Dyck PJ, Wang AK*, et al.* Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. New England Journal of Medicine. 2018;379(1):22-31.
4. Brannagan T, Wang AK, Coelho T, Cruz MW, Polydefkis MJ et al. Long-term update from the open-label extension of the NEURO-TTR study in patients with hereditary transthyretin amyloidosis [abstract] . Blood 2018; 132:498.

This assessment is based on data submitted by the applicant company up to and including 17 May 2019.

**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

Medicine 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 medicine 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 NHSScotland 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 NHSScotland 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.