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Advising on new medicines for Scotland
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telotristat ethyl 250mg film-coated tablets (Xermelo®)

SMC No 1327/18

Ipsen Limited

4 May 2018

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 NHS Scotland. The advice is summarised as follows:

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

telotristat ethyl (Xermelo®) is accepted for restricted use within NHS Scotland.

Indication under review: Treatment of carcinoid syndrome diarrhoea in combination with somatostatin analogue therapy in adults inadequately controlled by somatostatin analogue therapy.

SMC restriction: patients with CS diarrhoea who experience an average of four or more bowel motions per day, despite receiving somatostatin analogue therapy.

A phase III double-blind randomised study showed that telotristat ethyl produced a statistically significant greater reduction in the number of daily bowel motions in patients with carcinoid syndrome on stable dose somatostatin analogue therapy compared with placebo.

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

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

Chairman
Scottish Medicines Consortium

Published 11 June 2018

Indication

Treatment of carcinoid syndrome diarrhoea in combination with somatostatin analogue therapy in adults inadequately controlled by somatostatin analogue therapy. [1]

Dosing Information

The recommended dose is one 250mg tablet three times daily with food.

Available data suggest that clinical response is usually achieved within 12 weeks of treatment. It is recommended to reassess the benefit of continued therapy in a patient not responding within this time period.

See summary of product characteristics (SPC) for further information.[1]

Product availability date

26 September 2017

Telotristat ethyl has been designated an orphan medicine by the European Medicines Agency (EMA) and also meets SMC ultra-orphan criteria.

Background

Telotristat ethyl prevents serotonin biosynthesis through inhibition of peripheral enzymes; L-tryptophan hydroxylase 1 and 2. In patients with carcinoid syndrome (CS) serotonin is over secreted, resulting in altered gastrointestinal tract function, which may manifest as diarrhoeal symptoms and abdominal pain.[1] CS usually results from metastases of well differentiated neuroendocrine tumours (NETs) that over-produce serotonin and other neuroendocrine hormones. The higher levels of serotonin in circulation stimulate intestinal secretions and intestinal motility leading to diarrhoeal symptoms. Approximately 75% of patients with CS experience diarrhoea. Somatostatin analogues are commonly used for symptom control, including diarrhoeal symptoms. Unlicensed high doses of somatostatin analogues are used in patients with inadequate control, or loss of control, of symptoms when treated with licensed doses. Following somatostatin analogues, management approaches that remove or reduce the size of NETs, such as embolisation, radiotherapy, chemotherapy or tumour resection, may also stop or control symptoms.[2-4]

The submitting company has requested that SMC considers telotristat ethyl when positioned for use in patients with CS diarrhoea who experience an average of four or more bowel motions (BMs) per day, despite receiving somatostatin analogue therapy.

Telotristat ethyl 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

Following hepatic metastases of gastrointestinal NETs or the development of NETs in another organ system, neuroendocrine hormones avoid first pass metabolism, enter systemic circulation and produce the symptoms of CS which include diarrhoea and skin flushing. NET over-production of serotonin is the most likely cause of CS associated diarrhoea. High levels of serotonin may also be associated with fibrogenesis which can manifest in patients with CS as cardiac valvular fibrosis also known as carcinoid heart disease. Most NETs are more indolent than other malignancies; this can lead to a delay of up to seven years between the development of the first symptoms and diagnosis.[2 4]

Somatostatin analogues are the standard therapy for the treatment of CS symptoms. Patients with inadequate symptom control or loss of symptom control on licensed doses of long acting release octreotide or lanreotide depot are commonly prescribed more frequent administrations than licensed (every two or three weeks instead of every four weeks). There are currently no other licensed medicines for the treatment of CS diarrhoea. Alternative strategies to reduce symptoms associated with NETs involve reducing tumour burden.[2 4] Clinical experts consulted by SMC considered that there is an unmet need in this therapeutic area when patients report uncontrolled diarrhoea despite somatostatin analogue therapy. Telotristat ethyl meets SMC ultra-orphan criteria.

A patient and clinician engagement (PACE) meeting was held to consider the added value of telotristat ethyl in the context of treatments currently available in NHS Scotland. At the PACE meeting, attention was drawn to the small proportion of CS patients (possibly <30 in Scotland) who are affected by refractory diarrhoea and the unmet need due to the absence of other licensed treatments for this small patient group. This refractory diarrhoea, which is continuous, can have a major impact on patients' lives, causing physical and psychological distress through frequent trips to the toilet (possibly >10 times/day: approximately every one and a half waking hours). The refractory symptoms, which may also be associated with abdominal pain and fatigue, affect employability and family life as easy access to suitable toilet facilities when leaving their home can be a major hurdle and the associated planning, organising and stress is a big burden. The diarrhoea can come on without warning and be explosive: this may result in patients being reluctant to leave their home. Additional issues experienced by patients include weight loss, restricted diets, nutrition and skin problems. These patients may have a low quality of life and loss of dignity due to their symptoms and this can be compounded by comorbidities.

Impact of new technology

Summary of evidence on comparative efficacy

The primary clinical evidence comes from the pivotal study, TELESTAR, which was a phase III, international, multicentre, randomised, double-blind, study that compared two doses of telotristat ethyl with placebo in patients with inadequately controlled CS diarrhoea, despite receiving somatostatin analogue therapy.[3] Randomised patients met the following inclusion criteria; 18 years or older, had histopathologically confirmed well differentiated metastatic NETs with documented extent of disease based on imaging, a documented history of CS, a mean of at least four BMs per day during the study run-in period, treatment with stable dose somatostatin analogues (long-acting release, depot, or continuous infusion) for ≥3 months prior to enrolment,

receiving treatment with a minimum dose of long-acting release octreotide (30mg every four weeks) or lanreotide depot injection (120mg every four weeks), or highest tolerated dose of somatostatin analogue if not tolerating these minimum doses. All patients continued to receive their baseline dose of somatostatin analogue for the duration of the study. The use of rescue short acting octreotide and anti-diarrhoeal agents was permitted and unrestricted. The study included a three to four week run-in period to enable baseline symptoms to be determined. Following assessment for eligibility, 135 patients were randomised equally to telotristat ethyl 250mg or telotristat ethyl 500mg or placebo orally three times per day for the 12 week double-blind treatment phase. The 500mg dose of telotristat ethyl has not been licensed and therefore will not be discussed further. Randomisation was stratified by baseline urinary 5-hydroxyindoleacetic acid (u5-HIAA) level.[2 3]

The primary outcome was change from baseline in patient reported daily BM frequency averaged over the 12 weeks of the TELESTAR study and was analysed in the intention to treat population in the primary analysis.[2 3] The results of the primary analysis are presented in table 1 below.

Table 1. Change from baseline in number of bowel motions per day averaged over 12 week treatment period and estimate of difference from placebo in the intention to treat population.[2 3]

	Telotristat ethyl 250mg (n=45)	**Placebo (n=45)**
Mean baseline number of bowel motions/day (SD)	6.1 (2.1)	5.2 (1.4)
Mean change from baseline to week 12 of bowel motions/day (SD)	-1.4 (1.4)	-0.6 (0.8)
Hodges-Lehmann estimator of difference in bowel motions/day	-0.8 (97.5% CI: -1.3 to -0.3) p<0.001	

SD = standard deviation, CI = confidence interval

The mean change in u5-HIAA level from baseline was a secondary outcome. For patients randomised to telotristat ethyl 250mg the Hodges Lehmann estimate of difference was reported as -30mg/24 hours (97.5% CI: -56 to -8.1; p<0.001) when compared with placebo.[2, 3]

A reduction in mean BMs compared to placebo was observed at week 3 of the TELESTAR study.[2] The proportions of patients in the telotristat ethyl and placebo groups respectively reporting a mean reduction of at least one BM per day were 67% and 31%, and reporting a reduction of at least two BMs per day were 33% and 4.4%.[2 3] The proportion of patients with a durable response, defined as ≥30% reduction in daily number of BMs for ≥50% of time over the 12 weeks of the TELESTAR study, was 44% of patients in the telotristat ethyl 250mg group versus 20% of patients in placebo group. This difference was statistically significant.[2 3]

A *post-hoc* analysis of the TELESTAR study reported that rescue somatostatin analogues were used by 13% (6/45) of patients randomised to telotristat ethyl 250mg and 22% (10/45) of patients randomised to placebo. Concomitant narcotic analgesic use was reported by 29% and 16% patients, and concomitant anti-diarrhoeal use by 44% and 33% patients respectively.[5]

There was no statistically significant difference between the two groups in terms of cutaneous flushing episodes, abdominal pain (scores reported on an 11 point scale), stool consistency and nausea. For the secondary outcome based on 'urge to defecate' there was no statistically significant difference between the groups when the Hodges-Lehmann estimator method was applied, but there was a statistically significant difference with the generalised line model method favouring telotristat ethyl 250mg over placebo.[2 3]

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLC-C30) and EORTC gastrointestinal NET (EORTC GI.NET21) questionnaires were used to evaluate quality of life in the TELESTAR study. There was no statistically significant difference between treatment groups in mean change from baseline for global health status and most of the individual subscales of EORTC QLC-C30 questionnaire, with the exception of the diarrhoea and insomnia subscales, which favoured telotristat ethyl and placebo respectively. The EORTC GI.NET21 questionnaire favoured placebo in terms of disease-related worries.[2]

In an open label extension of the TELESTAR study patients were offered the unlicensed telotristat ethyl 500mg dose three times daily for 36 weeks. Results were generally in line with the TELESTAR study but should be interpreted with caution due to the dose used and the open label design.[2]

Summary of evidence on comparative safety

Adverse events (AEs) were reported as being similar in the telotristat ethyl 250mg and placebo groups included in the TELESTAR study. Any treatment-emergent AE was reported by 82% (37/45) of patients in the telotristat ethyl group and by 87% (39/45) of patients in the placebo group. Discontinuation due to a treatment-emergent AE was reported for 7% of patients in the telotristat ethyl group and 13% of patients in the placebo group.[2, 3]

AEs with an incidence of ≥5% in the telotristat ethyl and placebo groups respectively included; nausea (13% and 11%), abdominal pain (11% and 18%), headache (11% and 4%) and flushing (new or worsening) (7% and 4%). Raised liver function tests (increased gamma-glutamyl transferase) were reported in 8.9% of patients receiving telotristat ethyl compared to no patients receiving placebo.[3] Depression related adverse events were reported by 6.7% of patients in both groups during the TELESTAR study.[3]

A total of five deaths was reported during the TELESTAR study, all of which occurred in patients with advanced metastatic disease.[2, 3] Only one death was considered to be possibly treatment related and this was due to cardiac arrest in a patient randomised to telotristat ethyl 500mg.[2]

The SPC contains special warnings and precautions for the use of telotristat ethyl in patients with prior or treatment emergent hepatic impairment or depression and patients with treatment emergent constipation. [1]

Summary of clinical effectiveness issues

The submitting company has requested that SMC considers telotristat ethyl when positioned for use in patients with CS diarrhoea who experience an average of four or more BMs per day, despite receiving somatostatin analogue therapy. Patients in the TELESTAR study were treated with at least the maximum licensed dose of long acting somatostatin analogue. This approach is consistent with clinical practice in Scotland.[4] The results of the TELESTAR study do not allow

for the comparison of licensed dose somatostatin analogue plus telotristat ethyl with unlicensed high dose somatostatin analogue.

Telotristat ethyl 250mg three times a day reduced the frequency of BMs per day averaged over 12 weeks in CS patients with ≥4 BMs per day at baseline who were receiving concomitant stable dose somatostatin analogue therapy, by a statistically significant greater extent than placebo.[2 3] Additional analyses showed that fewer patients in the telotristat ethyl 250mg group required the use of rescue short acting somatostatin analogue than in the placebo group.[2, 3]

Limitations of the TELESTAR study include; higher proportions of patients in the telotristat ethyl group received concomitant medication, which may have contributed to controlling BM frequency, than in the placebo group during the double-blind treatment phase; patients in the placebo group appeared to have less severe baseline symptoms of CS: telotristat ethyl 250mg group versus placebo group: mean daily BM frequency (6.1 versus 5.2), mean daily skin flushing episodes (2.8 versus 1.8) and mean u5-HIAA (93 versus 81mg/24 hours); with the exception of u5-HIAA all assessments were self-reported and may have been at risk of bias; the reduction in BMs of patients in the placebo group was unexpected and the exclusion of patients with severe liver impairment may reduce the generalisablity of the TELESTAR results to the Scottish population, as in practice patients may have liver metastases and some may have existing or develop new, severe liver impairment. [2 3 5]

The reported magnitude of telotristat ethyl treatment difference over placebo appears small, -0.81 BMs/day, although it was statistically significant. A minimum clinically important difference has not been defined. The goal of treatment with telotristat ethyl is to improve symptom control by reducing bowel motion frequency, however, there was no statistically significant difference in quality of life measures, EORTC GI.NET21 and EORTC QLC-C30 global health status, between telotristat ethyl and placebo groups. Prior studies in patients with NETs, treated with somatostatin analogues, have shown no improvement in EORTC-QLQ-C30 global health scores. [2] It has been suggested that this tool may not be sensitive to this population. [3]

Telotristat ethyl provides an oral treatment option, with no increase in monitoring requirements and may delay the need for higher risk, invasive palliative procedures. It may reduce the need for the use of unlicensed high doses of somatostatin analogue and hospital admissions for uncontrolled symptoms. There is a lack of robust data on the long term benefits and risks of telotristat ethyl.

At the PACE meeting, it was suggested that at least one in five patients would be expected to get a highly meaningful benefit from treatment with telotristat ethyl. It was highlighted that future studies may show telotristat ethyl to have a favourable impact on preventing the development of carcinoid heart disease and small bowel fibrosis associated with CS. As noted above, the limitations of the quality of life collecting tools used in the TELESTAR study were considered to explain the lack of statistically significant difference between telotristat and placebo groups in terms of quality of life.

Patient and clinician engagement (PACE)

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

The key points expressed by the group were:

- A small proportion of patients are affected by refractory CS diarrhoea, it is an ongoing and extremely debilitating condition which has a major impact on patients' quality of life, resulting in physical and psychological distress. Some patients are reluctant to leave their home or travel due to their uncontrolled diarrhoea which may also be associated with abdominal pain, faecal incontinence, fatigue, malnutrition and mental health problems.

- There are currently no licensed medicines for patients with CS diarrhoea refractory to somatostatin analogue therapy and therefore there is an unmet need for these patients.

- Telotristat ethyl is anticipated to be associated with a considerable improvement in quality of life for a proportion of patients, through the reduction in frequency and severity of diarrhoeal symptoms. This may provide additional benefits to patients through a return of confidence in terms of engaging in socialising, working and exercising; as well as benefits in nutrition and mental health.

- It is an oral therapy, therefore patients won't need to leave their homes for administration of this medicine and may potentially require less frequent somatostatin analogue injections, which may reduce the demand on NET services.

- Telotristat ethyl has a favourable safety profile and has the potential to provide a bridge to another line of therapy for the management of underlying disease that a patient may not be fit enough to receive otherwise.

Additional Patient and Carer Involvement

We received a patient group submission from the NET Patient Foundation and the Ann Edgar Charitable Trust. The NET Patient Foundation is a registered charity and the Ann Edgar charitable Trust is a charitable trust. The NET Patient Foundation has received 14% pharmaceutical company funding in the past two years, including from the submitting company. The Ann Edgar Trust has not received any funding from pharmaceutical companies in the past two years. Representatives from both organisations 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 telotristat ethyl 250mg plus somatostatin analogue to somatostatin analogue alone in patients with CS diarrhoea inadequately controlled by somatostatin analogue therapy. The comparator appears reasonable based on SMC clinical expert feedback. The economic model consisted of a 12 week decision tree, which was used to assess response to treatment, followed by a long run Markov model with states consisting of remaining on treatment (if a 12 week responder), discontinue treatment due to loss of efficacy or adverse events, or death. The time horizon was 30 years, with a weekly cycle to estimate probability of long run discontinuation.

The clinical data for the 12 week response rates were from the TELESTAR study, with outcomes based on the durable response endpoint in this study of 44% for telotristat ethyl 250mg plus somatostatin analogue and 20% for somatostatin analogue alone. In the base case

it was assumed that response was achieved at 6 weeks. In the longer run analysis the model was informed by discontinuation rates for telotristat ethyl plus somatostatin analogue from the 36 week open label extension of TELESTAR, which used the unlicensed 500mg dose. As the extension phase was single arm the longer run discontinuation rates for the comparator were based on the TELESTAR 12 week reported rates. Based on these sources weekly discontinuation probabilities of 0.53% and 1.19% were applied for telotristat ethyl plus somatostatin analogue and somatostatin analogue alone respectively. On moving into the discontinue treatment state all patients were assumed to receive subsequent therapies which, after an initial period of non-response (of 0 to 56 days depending on the treatment), were assumed to restore patients to complete response. The use of subsequent therapies was based on the opinion of three clinical experts in Scotland, and consisted of the use of transarterial embolisation (TAE) in 48% of patients, everolimus in 27%, peptide receptor radionuclide therapy (PRRT) in 17%, transcatheter arterial chemoembolisation (TACE) in 5%, debulking surgery in 2%, and radiofrequency ablation in 2% of patients.

Mortality associated with CS after somatostatin analogue treatment was estimated for all patients, based on a clinical study of a somatostatin analogue sponsored by the company which contained overall survival data. The overall survival estimates were extrapolated by fitting parametric functions to the data and applied to the death state in the model.

Utility estimates for response and non-response outcomes were based on a published study reporting the disutility of grade 3 or 4 diarrhoea in NETS patients compared to patients with stable disease without the adverse event.[6] The values of 0.60 for grade 3/4 diarrhoea and 0.71 for stable disease from this study were used to reflect non-response and response utilities in the model. Disutilities for telotristat ethyl plus somatostatin analogue and somatostatin analogue adverse events have been included as well as those for adverse events related to subsequent therapies.

Costs included medicine acquisition costs, somatostatin analogue administration costs, monitoring costs and adverse event management costs.

Somatostatin analogue is based on that used in the clinical study (sandostatin LAR and somatuline autogel) and included a proportion of patients receiving above licensed doses. The company stated that clinical expert feedback indicated this reflects Scottish clinical practice in CS patients. The costs of subsequent therapies have been estimated from various sources including NHS reference costs for procedures such as TAE, TACE and RFA, or by clinical assumption for PRRT (estimated cost of £80,000).

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 NHS Scotland.

In the base case with the PAS applied, telotristat ethyl plus somatostatin analogue was estimated to be dominant (ie more effective and less costly) over somatostatin analogue alone (Table 2). As telotristat ethyl is associated with an additional medicine cost, the key driver of the estimated cost savings is that fewer patients in the telotristat ethyl group incur the cost of subsequent therapy due to being predicted to have died before they discontinued the original treatment. The estimated QALY gain is small since patients are assumed to have a complete response to subsequent therapy, so any QALY benefits for telotristat ethyl are based on better response rates and lower net QALY loss associated with adverse events, which are offset to some extent by a loss of QALYs due to access to subsequent therapies.

The base case results and key sensitivity and scenario analysis results are presented in Table 2.

Table 2: base case and key scenario analysis results

Scenario analysis	ICERs (with PAS)
Base case	dominant
Lower bound probability of discontinuation of somatostatin analogue (0.96% per week)	dominant
Upper bound probability of discontinuation of somatostatin analogue (1.43% per week)	dominant
12 week response rates for licenced SSA dose patients (42% TE+SSA vs 15% SSA)	dominant
12 week response rate for TE assumed to be 40%	dominant
80% of patients receive subsequent therapies	£25,192
PRRT costs estimated to be £60,000	dominant
Total costs of subsequent therapies -10%	dominant
Overall survival for CS based on Gompertz extrapolation (lower mortality than in base case Weibull)	dominant

QALY = quality adjusted life year, ICER = incremental cost-effectiveness ratio, PAS = patient access scheme, SSA = somatostatin analogue, TE = telotristat ethyl, PRRT = peptide receptor radionuclide therapy, TAE = transarterial embolisation, TACE = transcatheter arterial chemoembolization, CS carcinoid syndrome

There were a number of weaknesses and uncertainties in the economic analysis:

- The predicted long term cost savings of telotristat ethyl within the economic model are dependent on avoidance of subsequent, more expensive, therapies. The assumptions underpinning this have several weaknesses described below.

- There is high uncertainty over the mix and use of subsequent therapies, and the cost of these therapies. In requested scenario analysis, when only 80% use of the subsequent therapies is assumed the ICER increases to £25,192/QALY with PAS (Table 2). The assumption that subsequent therapies are 100% effective (combined with other simplifying assumptions regarding their use) is likely to be unrealistic, and whilst this contributes to low estimated QALY gains for telotristat ethyl, this assumption is an important contributor to the estimated net cost savings.

- Cost savings are highly sensitive to the long run relative discontinuation rates and sensitive to the relative short term response rates. The long term relative discontinuation rates are based on limited short term clinical data (with an unlicensed dose for telotristat ethyl), and only short term discontinuation data for the somatostatin analogue. There is therefore significant uncertainty arising from these inputs.

- The above uncertainty is compounded by uncertainty over the extrapolated mortality rate which impacts on whether patients continue on to subsequent therapies.

- The difference in utility associated with response versus no response of 0.11 may be overestimated as ‘response’ is associated with a reduction in bowel movements rather than being without diarrhoea. The small QALY gain may therefore be overestimated.

Impact beyond direct health benefits and on specialist services

At the PACE meeting, attention was drawn to the benefit patients, family and carers would obtain from a reduction in the psychological and physical burden associated with refractory CS diarrhoea. Family members and carers may see patients return to previous activities which can provide a psychological boost for them. Partners may be able to achieve uninterrupted sleep if night time symptoms are controlled, and reduced hospital admissions would be of benefit to patients, family and carers. Telotristat ethyl may help reduce the time burden on NET services through a reduction in the frequency of somatostatin analogue doses and a reduction in the number of phone calls from distressed patients and carers, as well as organising previously unplanned appointments.

Costs to NHS and Personal Social Services

The submitting company estimated there would be 29 patients eligible for treatment with telotristat ethyl in year 1, rising to 51 patients in year 5. The estimated uptake rate was 10% in year 1 (3 patients) rising to 50% in year 5 (26 patients).

The submitting company did not estimate any costs outside the NHS.

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.

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

Conclusion

The Committee considered the benefits of telotristat ethyl in the context of the SMC decision modifiers and agreed that as telotristat ethyl 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 accepted telotristat ethyl for restricted use in NHS Scotland.

Additional information: guidelines and protocols

The Scottish Neuroendocrine Tumour Group published ‘Consensus guidelines for the management of patients with neuroendocrine tumours’ in February 2015 and updated the guidance in July 2015. The guideline was developed by NHS Scotland, with financial support for publication provided by Novartis. The recommendations relevant to symptom control include; all

patients with NETS should be discussed by a specialist NET multidisciplinary team, somatostatin analogues are the first line option for the medical management of symptomatic NETs, treatment should be initiated with the maximal dose of long acting somatostatin analogues but subcutaneous somatostatin analogue may be required in patients with severe symptoms, patients who fail to tolerate somatostatin analogue therapy should be considered for second line therapy with interferon alpha. Interventional radiology and radionuclide therapies are also discussed as management options. Everolimus and sunitinib are treatment options for unresectable and well differentiated pancreatic NETs.[4]

The UK and Ireland Neuroendocrine Tumour Society (UKINETS) published Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs) [7] in January 2012. Novartis Pharmaceuticals UK Ltd and Ipsen UK provided unrestricted educational grants for the original working party meeting. Novartis Pharmaceuticals UK Ltd also provided financial assistance to allow Porterhouse Medical Ltd, a medical writing agency, to aid the drafting of the guideline. The guidance does not make any recommendations regarding the management of CS but notes that "SSAs [somatostatin analogues] are effective in the management of the symptoms of carcinoid syndrome. Most studies report improvements in diarrhoea and flushing in 60 to 70% and 70 to 80% of patients, respectively, and a significant reduction (>50%) in biochemical markers (especially 5-HIAA) in 40 to 60% of patients." The guidance also advises that interferon alpha can be used on its own or added to a long acting somatostatin analogue if CS symptoms are not responding to the maximum dose of somatostatin analogues. The choice of treatment should be based on stage of disease, secretory profile and histology of the tumour as well as symptoms. Treatment options include radionuclide therapy, ablation, embolisation, chemo-embolisation and chemotherapy.

The European Neuroendocrine Tumour Society (ENETS) published Consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site[8] in April 2016. The guidance advises the use of long acting somatostatin analogues as first line therapy in patients with CS and that in cases of refractory symptoms of CS unlicensed high doses can be used, normally by reducing the time between doses from 4 weeks to 3 weeks.

ENETS published Consensus guidelines for the standards of care in neuroendocrine neoplasms: Systemic therapy - biotherapy and novel targeted agents[9] in September 2017. The guidance recommendations for the use of somatostatin analogues are generally in line with the ENETS consensus guideline 2016. It suggests that if an immediate effect is required, "rescue" octreotide may be used on an as-required basis. In addition it advises that Interferon-α2b is used as an add-on therapy to somatostatin analogue in refractory carcinoid syndrome or if somatostatin analogues are not suitable (e.g., negative somatostatin receptor status) or not tolerated.

Additional information: comparators

Telotristat ethyl would not replace another medicine. It would be used in addition to a somatostatin analogue.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Telotristat ethyl	**250mg orally three times a day**	**13,589**

Costs from eVadis on 05/12/2017. Costs do not take any patient access schemes into consideration.

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This assessment is based on data submitted by the applicant company up to and including 16 March 2018**.**

**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

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 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.