National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Anamorelin for treating cachexia and anorexia in people with non-small-cell lung cancer

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	British Thoracic Oncology Group	The topic is highly appropriate for appraisal by NICE as (1) NSCLC is one of the commonest cancers in the UK and a leading cause of death and morbidity; (2) cancer-related cachexia is a significant determinant of survival, morbidity and probably also of tolerability to anti-cancer treatments; (3) current pharmacological and non-pharmacological interventions are either of limited efficacy and utility (such as assisted nutrition) or have a poor evidence base or carry significant toxicity (such as corticosteroids and other appetite stimulants).	Comment noted. No action required.
	British Thoracic Society	This is a welcome development as cachexia in lung cancer is common and there is no current effective treatment.	Comment noted. No action required.
	Chugai Pharma	Yes - Cancer anorexia and cachexia associated with non-small cell lung cancer (NSCLC) is a multifactorial syndrome which leads to progressive functional impairment and a poor quality of life. In the UK there currently are no licensed treatments for this condition, which occurs in approximately 61%	Comment noted. No action required.

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		of non-small cell lung cancers and is accountable for around 20% of all cancer deaths**.** .(1) 1 Tisdale MJ, Nature Reviews Cancer, November 2002	
Wording	British Thoracic Oncology Group	The scope should reflect more strongly the consequences that cachexia has on the cancer patient's general health status, including psychological and social as well as physical functioning, quality of life and body image as well as on survival.	Comment noted. The scope is intended to provide a brief overview of the condition. No action required.
	Chugai Pharma	Suggested remit reflects submitted indication to EMA. Suggestion: [redacted]	Comment noted. The wording of the remit has been updated accordingly.
Timing Issues	British Thoracic Oncology Group	Current treatments are mostly either ineffective or carry significant toxicities in longterm use; a new approach is urgently needed.	Comment noted. If this appraisal is referred to NICE, it will be scheduled into the appraisal programme with consideration of the need to provide timely guidance.
	Chugai Pharma	Normal	Comment noted. No action required.

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Additional comments on the draft remit	British Thoracic Oncology Group	In the background, it would be helpful to give one year (or median) survival figures for NSCLC, as the 5 year survival rates are so poor that it may give the impression that it is 'not worth' investing in new supportive care technology for this group of patients.	Comment noted. To make the scope as succinct as possible, survival rates have been removed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	British Thoracic Oncology Group	It would be helpful to give one year (or median) survival figures for NSCLC, as the 5 year survival rates are so poor that it may give the impression that it is 'not worth' investing in new supportive care technology for this group of patients. It is also noteworthy that the current pharmacological approaches are not only poorly evidence based but also carry significant toxicities and mortality of their own.	Comments noted. To make the scope as succinct as possible, survival rates have been removed.
	Chugai Pharma	The background information section looks accurate and mostly complete. A suggestion would be to add into the final paragraph on Pharmacological treatment, a comment saying that there are no licensed pharmacological treatments for cancer related anorexia, cachexia or unintended weight loss in NSCLC in the UK. Suggest also highlighting the following: Nutritional screening and assessment are recommended at initial diagnosis, before cancer treatment begins, and should continue throughout care.(1)	Comments noted. The scoping document only provides a very brief summary of the condition and its management.

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		Suggest highlighting the following within the background information: Weight loss also has a significant effect on quality of life, and can be a major source of distress for patients and caregivers.(2,3) The psychosocial effects can include loss of independence, sense of failure, sense of helplessness, conflict with family members over food, social isolation and thoughts of death.(4) As well as reduced quality of life, cancer patients experiencing weight loss leading up to and during chemotherapy receive a lower initial dose and experience more frequent and severe dose-limiting toxicity when compared to weight-stable patients(5,6), consequently receiving significantly less treatment.(7)These patients also experienced decreased quality of life, performance status and survival intervals and lowered response to treatment. A reduction in the occurrence or progression of cancer cachexia would have several flow-on effects in terms of health economic outcomes, for example, reduced hospital admissions for adverse effects of cachexia, shorter hospital stays due to greater capacity to regain health sooner or maintain health longer and reduced attendance to emergency departments for cachexia-related complications.(8) *[References provided but not reproduced here.]*	
The technology/ intervention	British Thoracic Oncology Group	Yes	Comment noted. No action required.
	Chugai Pharma	Suggested alterations in green: Anamorelin (Adlumiz) is a first-in-class, ghrelin receptor agonist. Ghrelin is the endogenous ligand for the G-protein-coupled ghrelin receptor, (formerly known as the growth hormone secretagogue receptor). Ghrelin possesses	Comment noted. The technology section of the scope has been amended accordingly.

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		anabolic, appetite-enhancing, anti-inflammatory and gastro-intestinal stimulant properties, including regulation of glucose metabolism. Anamorelin is administered orally once daily. Anamorelin does not currently have a UK marketing authorisation for treating anorexia, cachexia or unintended weight loss in adult patients with NSCLC. It has been studied in clinical trials compared with placebo in adults with anorexia and cachexia associated NSCLC.	
Population	British Thoracic Oncology Group	Yes – but should qualify 'cachexia' as early (<5% weight loss), moderate (5-9% weight loss) or severe (>9% weight loss) as these have prognostic importance and may respond differently to interventions.	Comment noted. Consultees at the workshop agreed that these subgroups should be included in the scope. We heard that there are no well-established definitions of early/moderate/severe cachexia, so the scope will not attempt to define these categories. The appraisal committee will discuss how to define the subgroups.
	Chugai Pharma	Suggested alteration to population: Adults with NSCLC and anorexia, cachexia or unintended weight loss.	Comment noted. The definition of the population in the scope

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			has been amended accordingly.
	Chugai Pharma	The following subgroups were submitted to the EMA as part of the regulatory process • [redacted]	Comment noted. Consultees agreed that body mass Index and weight loss were important subgroups but the exact criteria would be trial specific and so the scope will not attempt to define these categories. It was agreed that Anorexia/Cachexia Subscale (FAACT) ≤30 was an important subgroup. It was agreed that C-reactive protein would not be considered on its own because there are several inflammatory markers. In conclusion it was agreed that the scope should include subgroups defined by severity of cachexia, body mass index and

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			score on the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire.
Comparators	British Thoracic Oncology Group	Should specify against placebo. It will be difficult to find direct evidence to compare with current treatments.	Comment noted. Placebo is not a relevant comparator for a NICE appraisal (because it is used in clinical trials and not in routine practice). The consultees agreed that 'established clinical management without anamorelin' was the relevant comparator.
	Chugai Pharma	There is a lack of clear guidance for the management of anorexia and cachexia in cancer patients. The European Palliative Care Research Collaborative (EPCRC) have produced a consensus and evidence-based clinical practice guideline for the management of cancer cachexia in advanced cancer patients, with a focus on refractory cachexia, for all health professionals involved in the provision of palliative care and in the care of patients with advanced cancer(1). Cachexia can be clinically refractory as a result of very advanced cancer (pre-terminal) or the presence of rapidly progressive cancer unresponsive to anticancer therapy, in this stage reversal of weight loss seems no longer possible. In refractory cachexia the burden and risk of artificial nutritional	Comments noted. The consultees at the scoping workshop agreed that current established care includes dietary advice and nutritional supplements. Some patients also have short-term corticosteroids (such as

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		support are likely to outweigh potential benefits, thus therapeutic interventions focus typically on alleviating suffering associated with cachexia, such as symptom control with appetite stimulation and treatment of nausea or eating related-distress of patients and families. It may often be the overall medical condition of the patient rather than the severity of the cachexia that may render them refractory.(1,2) There is no clear consensus within the NHS for the clinical management of anorexia and cachexia, but clinical opinion gathered within a recent advisory board suggests that current care is broadly in alignment with the following multimodal approach: • Referral to dietician for nutritional counselling and possible intervention with nutritional supplements. In extreme cases enteral tube feeding or parenteral feeding is utilised – this is clinically viewed as an expensive and largely futile activity. A Cochrane Review on the use of Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for treatment of cancer cachexia found there was insufficient data to establish whether oral EPA was better than placebo.(3) • Short term treatment with steroids such as dexamethasone - this is not used to treat cachexia and increase weight; rather to help manage chemotherapy and improve performance status • Usage of megestrol acetate is limited due to Cochrane Review which showed poor efficacy on lean body mass; it also carries significant risk of mortality(4) • Cannibinoids such as tetrahydrocannabinol (THC) may increase appetite in selected patients, although there is not robust evidence to support their use and they are not recommended in the EPCRC guidelines (1) • Cytokine antagonists may be considered as pro-inflammatory cytokines play a role in the inflammatory reaction underlying cancer cachexia.	low-dose dexamethasone) or progestins. The consultees agreed that 'established clinical management without anamorelin' was the relevant comparator for the scope.

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		A Cochrane Review on Thalidomide for managing cachexia in advanced cancer found inadequate evidence to recommend it for clinical practice[5], and this class of molecule are not recommended in the EPCRC guidelines [1] • Non-Steroidal Anti-Inflammatory drugs used in isolation are seen to offer little benefit but may be more effective as part of a multi-modal intervention [1] • Metoclopramide has shown efficacy in treating nausea and early satiety in cancer patients with cachexia, although extrapyramidal side effects have been noted. There is no evidence showing prokinetics improve the nutritional states of patients with advanced cancer or refractory cachexia [1] Evidence available for the effectiveness of these interventions is exceedingly sparse. As no treatments are currently available with proven effectiveness, patients generally are not assessed until later down the line, their cancer has advanced and the complicated condition of the patient means the effectiveness of treatments is diminished. Contrary to how anorexia cachexia is currently being managed in today's clinical practice, clinical advisors consulted indicated a much earlier use for anamorelin. This is in line with published expert opinion of cachexia treatment in general. "If effective therapies emerge, early detection of malnutrition and cachexia will be increasingly important in the hope that timely intervention can improve both patient-centred and oncology outcomes"[6] The range of health care practitioners involved in treatment is also varied and includes oncologists, palliative care specialist's, dieticians, nurses, surgeons and GP's. *References provided but not reproduced here.*	

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Outcomes	British Thoracic Oncology Group	Lean body mass is appropriate but should specify how this will be measured – eg CT muscle mass at L3 level, DEXXA. How will 'increased muscle strength' be measured? Should specify objective measures as grip strength, walking test. The term' mortality' is ambiguous as it could cover both the cancer-related survival (which is admittedly partly determined by extent of cachexia at diagnosis), or mortality arising from treatment related toxicity.	Comments noted. Appropriate methods to measure outcomes listed in the scope will be considered during the appraisal. Attendees at the workshop noted that overall survival was a secondary outcome in the anamorelin clinical trials, and as cachexia is responsible for 20% of cancer deaths, treatment with anamorelin could plausibly extend overall survival. Consultees therefore agreed that the outcome mortality should be retained, but would be written as 'overall survival' for consistency with other NICE scopes.
	British Thoracic Society	We suggest removal of mortality as an outcome measure as the aim of treatment is to improve QoL.	Comment noted. See above response.

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	Chugai Pharma	The outcomes presented represent those most relevant to clinical practice with the exception of muscle strength. There has been significant debate on the value of measuring and how to measure muscle strength and function in cancer cachexia(1) Previous studies of the mechanical quality of muscle in cancer patients have shown that this is variable and tends to be low(2). These findings suggest that preservation/augmentation of lean mass (which includes muscle mass) does not necessarily always translate into a direct and measurable functional benefit if other factors remain unchanged. In other words, if certain aspects of the cachexia syndrome remain unmodified (e.g. underlying systemic inflammation or physical inactivity), the wider clinical and subjective impact of unimodal interventions (e.g. drug-induced muscle anabolism) may be less evident. Thus a considered view of the outcome of the ROMANA studies is not that the co-primary endpoint was not met but that the model of linking lean mass (of which the largest component is skeletal muscle) and strength together needs to be reconsidered and that the outcomes for lean body mass and strength should be considered separately. *References provided but not reproduced here.*	Comments noted. Attendees at the scoping workshop noted that muscle strength was the co-primary endpoint in the clinical trials and should be included in the scope.
Economic analysis	British Thoracic Oncology Group	The time horizon should reflect the typical life expectancy, ie 1-2 years or median survival for different subtypes of NSCLC.	Comment noted. No action required.
	Chugai Pharma	We would propose to conduct economic analysis using the clinical trial data available for anamorelin vs placebo in the ROMANA clinical trial programme. Patients within the ROMANA trials received 1 course of anamorelin (12 weeks) and were then able to enrol into an extension study for a further 12 weeks of treatment. These data include follow-up of 52 weeks for overall survival.	Comment noted. No action required.

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		We would propose to model outcomes in terms of costs, quality of life and survival based upon patient response to treatment – this is most likely to be measured in terms of the trial primary endpoint lean body mass (LBM); consideration is also being given to modelling according to response in terms of body weight. A simple Markov model structure is proposed in line with the trial evidence available. A lifetime horizon is likely to be most appropriate for the economic model as differences in mortality have been observed for patients with LBM response compared to those with no LBM response. EQ-5D and resource use data were collected within a subset of patients within the ROMANA trials (n=96). It is proposed to use these EQ-5D data to define a mapping algorithm from the more widely collected anorexia cachexia specific questionnaire (FAACT) included within the full trial population. Resource use data collected within the subset of patients in the ROMANA trials are unlikely to be fully generalizable to UK practice (collected in Poland & Hungary) therefore resource use estimates will most likely be loosely informed by clinical trial with UK clinician input. The following costs are expected to be included within the economic model: - Costs of treatment for anorexia cachexia - Costs of any side effects of treatments (likely limited given side effect profile of anamorelin) - Cost of routine appointments for treatment of anorexia cachexia (e.g. dietician appointments) - Cost of hospitalisation related to anorexia cachexia (if possible) Costs will be applied from a UK NHS perspective using standard UK cost sources.	

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Equality and Diversity	British Thoracic Oncology Group	Patient who are referred at an earlier stage to palliative care services could be excluded from receiving anamorelin if the drug is actually or seen to be restricted to use within oncological services. NICE should therefore look for evidence of use of anamorelin in clinical trials for patients who were recruited from palliative care services, or where such patients were excluded.	Comment noted. NICE technology appraisal guidance does not typically restrict the setting in which a drug can be prescribed, unless such a restriction is included in the marketing authorisation or is proposed by consultees.
	Chugai Pharma	No proposed changes to be made.	Comment noted. No action required.
Other considerations	Chugai Pharma	Weight loss is a key indicator of anorexia cachexia, however, the patients subjective experience is also a key factor • Patient's own view of weight loss and lack of appetite • General mood and well-being – anorexia cachexia can be extremely isolating for patients • Family perspective is also taken into some consideration Key goals of treatment for anorexia cachexia are: • Weight gain and appetite • Overall well-being and mood • To allow ongoing treatment for NSCLC	Comment noted. The appraisal committee will discuss the outcomes that are important to patients.

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		• Improve other clinical symptoms • Improvement in fatigue / energy Market research[1] has shown that patients access multidisciplinary teams such as oncology, palliative care, dietetics and research has shown that patients access primary care services when worried about weight loss. Suggest that the impact on primary care is considered in the proposed appraisal. The regulatory submission for anamorelin included evidence at 12 weeks from ROMANA 1&2, with a further 12 weeks of treatment possible for patients entering ROMANA 3. No fixed treatment duration has currently been decided.	
Innovation	British Thoracic Oncology Group	This is a first in class drug and could have significant impact alongside, or replacing some existing pharmacological approaches that are poorly evidence based. Studies should have included HRQOL as an important outcome measures. These should be included in the QALY calculation	Comment noted. No action required.
	Chugai Pharma	Anamorelin can be considered innovative as it is first in class and will be the first licensed pharmacological treatment for anorexia, cachexia or unintended weight loss in adult patients with NSCLC, where treatment options are limited. Expert opinion suggests that cancer cachexia cannot be fully reversed by nutritional support alone [1]. The current EPCRC guidelines suggest a multimodal treatment approach should be employed, including pharmacological and non-pharmacological interventions, such as nutritional supplements, nutritional support and exercise [2]. However, there are no licenced pharmacological therapies for cancer cachexia. Evidence from the ROMANA trial program shows that patients treated with anamorelin have a significant improvement in signs and symptoms of	Comment noted. No action required.

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		anorexia cachexia in NSCLC, including lean body mass, body weight, appetite and quality of life, with a well-tolerated safety profile versus placebo. UK clinicians consulted have indicated that anamorelin, as an effective pharmacological therapy, is a step change in the management of anorexia cachexia and may lead to improved outcomes from the chemotherapies used to treat NSCLC. The following benefits are unlikely to be easily captured within standard QALY calculations: - Impact of anamorelin (and anorexia cachexia) on fatigue – there are known issues in the ability of the EQ-5D questionnaire to quantify the impacts of fatigue on patient quality of life. Fatigue is a key symptom of anorexia cachexia. The ability of the EQ-5D to capture benefits to patients from an increase in appetite is also largely unknown - Impact of treatment on families and caregivers – anorexia cachexia has a large impact on families as well as the patient Data from the anorexia cachexia domain of the FAACT questionnaire is available to quantify the impact of anorexia cachexia on patient quality of life including on appetite. FACIT-F specifically addresses physical and functional consequences of fatigue.[(3)] No direct trial data are available to quantify the impact of anorexia cachexia on the quality of life of families or caregivers. *References provided but not reproduced here.*	
Questions for consultation	British Thoracic Oncology Group	Anamorelin should be included within a new section on the NICE Lung cancer pathway, section on 'Supportive and palliative care'	Comment noted. No action required.

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	Chugai Pharma	Where do you consider anamorelin will fit into the existing NICE pathway, NICE Pathway: Lung cancer" Anamorelin fits into the existing NICE Clinical Guideline No 121, April 2011 "Lung cancer: diagnosis and management" in section 1.5.18 "Managing other symptoms: weight loss, loss of appetite, difficulty swallowing, fatigue and depression 1.5.18 Other symptoms, including weight loss, loss of appetite, depression and difficulty swallowing, should be managed by multidisciplinary groups that include supportive and palliative care professionals. [2005]" In NICE Pathway: Lung cancer, March 2012, NICEguideline CSG4 2004 is referenced within the supportive and palliative care path. CSG4 advises that people with advanced cancer should have access to a range of services to improve their quality of life. CSG 4 does not specifically discuss quality of life in relation to weight loss in cancer however this is a distressing complication of many cancer types including NSCLC for patients, carers and family. For future revisions of CSG4 this could be a consideration for inclusion.	Comment noted. No action required.
Additional comments on the draft scope	None		

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
Primary Care Respiratory Society
Royal College of Nursing