National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Masitinib for treating unresectable or metastatic gastrointestinal stromal tumours after treatment with imatinib

Response to consultee and commentator comments on the draft remit and draft scope

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	AB Science	Yes	Comment noted.
	GIST Support UK	This is relevant and appropriate but we feel is premature, as there are not enough results from trials data.	Comment noted.
	Pfizer	This appraisal is appropriate.	Comment noted.
	Sarcoma UK	Yes	Comment noted.
Wording	AB Science	Yes	Comment noted.
	GIST Support UK	The remit gives a good background commentary to the current treatment status of GIST. It goes on to a good summary of the considerations that should be taken into account. However, it is difficult, at this stage, to say much about the cost effectiveness of the proposal as we do not yet have enough trials evidence or manufacturers costs of the product.	Comment noted.
	Pfizer	Consistent with what's in the public domain about masitinib's potential licensed population.	Comment noted.
	Sarcoma UK	Yes - although this is subject to the final licensed indicaton.	Comment noted.
Timing Issues	AB Science	[redacted]	Comment noted.

Section	Consultees	Comments	Action
	GIST Support UK	Probably too premature, we need the trials data and cost of the drug from the manufacturers.	Comment noted. In order to produce timely guidance to the NHS, NICE aims to hold the first Appraisal Committee meeting close to the expected marketing authorisation.
	Pfizer	No known urgency.	Comment noted.
	Sarcoma UK	As soon as possible following licensing	Comment noted. In order to produce timely guidance to the NHS, NICE aims to hold the first Appraisal Committee meeting close to the expected marketing authorisation.
Additional comments on the draft remit	GIST Support UK	On the terminology ie c-Kit, KIT or CD117 as stated in the remit, it will probably be difficult to get a concensus as different groups of stake holders use the different terms. Perhaps NICE and their advisors need to provide a lead on this. However, all are in usage and perhaps for a rare condition which is little known it is wise to use as many as possible.	Comment noted.

Section	Consultees	Comments	Action
	Sarcoma UK	We understand that regorafenib is being considered for marketing authorisation by EMA for the same stage in the GIST patient pathway. Is an appraisal of this technology being considered ?	Comment noted. Masitinib is being appraised through the single technology appraisal process.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	AB Science	Yes	Comment noted.
	GIST Support UK	Background information is a good summary	Comment noted.
	Pfizer	No comment	Comment noted.
	Sarcoma UK	The mutation variations present in GIST are significantly simplified in this statement. What should be added is that it is now evident that there is a far larger proportion of patients with rare mutations, or with no identified mutations, than previously thought. Numbers are very small but the standard treatments in both first and second-line are often ineffectual. It is also clear that patients develop secondary mutations which are resistant to imatinib treatment. Because identification of these mutations is problematic (biopsy is usually inadvisable) TKIs with different modes of activity are needed.	Comment noted. Please note the background section is a brief description of the disease area. No change to the scope required
The technology/ intervention	AB Science	Yes The best terminology to be used is c-Kit.	Comment noted.
	GIST Support UK	The Company involvement in the manufacture of Masitinib should/will make sure that formulations are correct to give maximum benefit to patients	Comment noted.
	Pfizer	No comment	Comment noted.
	Sarcoma UK	Yes	Comment noted.

Section	Consultees	Comments	Action
Population	AB Science	Yes Significant benefit observed in OS in overall population and in the subgroup of patients previously treated with 400mg of imatinib. Improved OS was observed in other subpopulations (c-Kit exon 9, c-Kit exon 11, patients previously treated with 800mg of imatinib) Benefit in PDGFR subpopulation was not assessed due to small number of patients.	Comment noted. If evidence allows, subgroups according to the tumour genetic mutational status will be considered during the appraisal to identify which patients are likely to experience a greater benefit from treatment.
	GIST Support UK	Ideally we need to target appropriately identified mutational groups according to experimental/trials data either already published or to be published. Otherwise some groups of GIST patients may receive treatment which is ineffective for them.	Comment noted. If evidence allows, subgroups according to the tumour genetic mutational status will be considered during the appraisal to identify which patients are likely to experience a greater benefit from treatment.
	Pfizer	Consistent	Comment noted.
	Sarcoma UK	Yes. It should be noted that it may be appropriate for masitinib and sunitinib to be 2nd/3rd line - ie. used in succession.	Comment noted.
Comparators	AB Science	Yes, sunitinib is the best and only comparator in 2nd line of treatment. Consequently, there is no need to compare with best supportive care	Comment noted.
	GIST Support UK	Yes	Comment noted.
	Pfizer	Sunitinib is an appropriate comparator.	Comment noted.

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	Sarcoma UK	To cover the whole patient group with one comparator is problematic. Sunitinib is the standard of care for most of these patients. High dose imatinib (800mg/d) may be more appropriate for some patients (eg. those with Exon9 mutation). This was not appraised by NICE in TA209 (see para 4.1.10) despite presentation of published meta-analysis data by physicians and patient groups. As noted above the nature of sunitinib and masitinib is that they could be successive therapies, they are not alternatives which exclude each other.	Comment noted. The technology will be appraised in line with its UK marketing authorisation.
Outcomes	AB Science	Yes (should be completed with TTF)	Time to treatment failure has been added to the list of outcomes.
	GIST Support UK	Until evidence is published this remains unknown, but we would prefer Progression Free Survival (PFS) to Overall Survival (OS), as we feel that this is a much more timely outcome measure (OM), and in this older group reflects the reality that treatments may delay disease progression, but death from all causes is more common than in the overall population.	Comment noted.
	Pfizer	The phase 2 trial comparing mastinib with sunitnib was an extremely small trial with N=44 and it is difficult to draw any conclusions from such a small number of patients. In addition, this was a trial in which patients on the masitinib arm were able to cross over to the Sutent arm and receive an active treatment, whereas patients in the sunitnib arm were not able to cross over and received only BSC. Therefore, this is not a head to head trial, comparing two agents, but in fact a trial comparing sequencing of 3 TKIs vs 2 TKIs in metastatic or inoperable GIST (Adenis et al, J Clin Oncol 30, 2012 (suppl; abstr 10007).	Comment noted. The Committee will consider the availability, nature and quality of the clinical evidence during the course of the appraisal
	Sarcoma UK	A simplistic view of the patient pathway of this disease should be avoided. The measures indicated are appropriate, however analysis of both progression free and overall survival may be confounded by surgical treatment when stable disease has been attained.	Comment noted.
Economic analysis	AB Science	na	Comment noted.
	GIST Support UK	Too soon to be able to comment as there is no final price yet known for humans - we only have veterinary data (dogs) at present.	Comment noted.

Section	Consultees	Comments	Action
	Pfizer	No comments	Comment noted.
	Sarcoma UK	None	Comment noted.
Equality and Diversity	AB Science	No discrimination is envisaged	Comment noted.
	GIST Support UK	Children and young adolescents are generally excluded from clinical trials. Masitinib may prove useful for paediatric GIST patients who have an unmet clinical need in this indication.	Comment noted. The technology will be appraised in line with its UK marketing authorisation. The population in the clinical trials for masitinib does not include children and young adolescents. This means that the population of children and young adolescents is likely to be outside the scope of the proposed NICE appraisal. No change to the scope required
	Pfizer	No comments	Comment noted.
	Sarcoma UK	None	Comment noted.

Section	Consultees	Comments	Action
Innovation	AB Science	Yes Significant benefit was observed in overall survival, safety (see document attached – confidential data). In a phase II clinical trial, superiority of masitinib over sunitinib was evidenced by a significant benefit in OS in masitinib treated patients vs sunitinib treated patients (median OS higher than 21 months (median not reached (95% CI [21.2; NR])) versus 15.2 months (95% CI [9.4; 21.7]), respectively at the date of cut-off analysis (January 31st 2012). This corresponded to a statistically significant hazard ratio of 0.29 (95% CI [0.10; 0.85], *p*-value=0.016). Safety analysis of masitinib in this phase II study demonstrated that masitinib has a better safety profile than sunitinib in GIST patients under prior progression with imatinib evidenced by a statistically significantly: . lower occurrence of suspected non-fatal serious adverse events (0% vs 19.0%, respectively, *p*-value=0.044), . lower occurrence of related non-hematological grade 3 and any grade 4 adverse events (17.4% vs 57.1%, respectively, *p*-value=0.011), . longer Safety Event Free Survival (9% vs 52.4%), respectively, *p*-value ≤ 0.001). in masitinib-treated patients as compared with sunitinib-treated patients. See document attached for more details	Comment noted. The manufacturer is encouraged to describe the innovative nature of masitinib in their evidence submission. Specifically, how innovative is masitinib in its potential to make a significant and substantial impact on health-related benefits, and whether any potential significant and substantial health−related benefits that have been identified were not included in the economic model. The Committee will consider this information during the course of the appraisal. No change to the scope required.
	GIST Support UK	Maisitnib has the potential to make a big difference to patients who do not benefit from current available treatments eg Paediatric, wild type patients and some with imatinib resistent mutations, also possibly secondary mutations which do not respond to current therapies.	Comment noted.
	Pfizer	No comments	Comment noted.

Section	Consultees	Comments	Action
	Sarcoma UK	The challenge of treating advanced GIST has changed rapidly over the last few years and the pace of change is not slowing. Much of this advance is being informed by growing understanding of mutations, by the benefits being achieved from adjuvant therapy with imatinib, by understanding issues raised by the withdrawal of treatment with TKIs, by the use of surgery with stable disease after treatment with both imatinib and sunitinib, and with better understanding of side effects resulting in reduced use of inappropriate doses and treatment withdrawal. Presenting a new TKI treatment into this mix creates the potential for more patients to benefit from these other innovations. Data are mostly presented as small case series owing to the small numbers of patients and the impossibility of conducting RCTs. One RCT (EORTC 62063) for surgery of residual disease was abandoned owing to the impossibility of recruiting patients.	Comment noted.
Other considerations	AB Science	Na	Comment noted.
	GIST Support UK	Mutational analysis should be mandatory for all GIST patients, including paediatric GIST. This could eventually lead to much more targetted treatment with Masitinib, if it is eventually deemed useful. It is likely to be far more cost effective in the long run to perform mutational analysis and identify which patients will benefit from which therapies.	Comment noted.
	Pfizer	No comments	Comment noted.
	Sarcoma UK	We understand that regorafenib is being considered for marketing authorisation by EMA for the same stage in the GIST patient pathway. Is an appraisal of this technology being considered ?	Comment noted. Masitinib is being appraised through the single technology appraisal process.
Questions for consultation	AB Science	Already responded	Comment noted.
	GIST Support UK	Most points are covered above.	Comment noted.

Section	Consultees	Comments	Action
	Pfizer	Sunitinib is the most routinely used treatment in this patient population in UK and the only therapy approved by NICE in second line. Best supportive care is not routinely used in second line and therefore should not be regarded as a comparator. Sutent has proven efficacy across all commonly occurring mutations in GIST (KIT exon 9, KIT exon 11, and wild-type KIT/PDGFRA and has shown superior efficacy particularly in patients with an exon 9 mutations in c-kit in terms of PFS and OS. There is currently no evidence available in the public domain or through peer reviewed publications as to the efficacy of Masitinib based on the occurance of different mutations in GIST (Heinrich,et al J Clin Oncol 26:5352-5359). The STA process is the appropriate way to appraise masitinib.	Comment noted. Comment noted Comment noted
	Sarcoma UK	Sunitinib and 'best supportive care' are the most appropriate comparators. However we understand that regorafenib is being evaluated for licensing by EMA and this would be for a similar place in the patient pathway for advanced GIST. The distinction between 2nd and 3rd line (following 1st line imatinib) has become blurred as TKIs with different modes of action are all appropriate meaning that a succession of treatments is feasible. This succession can best be determined on a patient-by-patient basis. Both c-KIT and KIT are in general use while CD117 is acceptable though less frequently used. There is one small group which requires careful attention, although there are no data with regard to this technology. Wild-type GIST (no identifiable mutation) affects younger patients, mostly female, some of whom will require treatment as adults. Current TKI treatments have little efficacy.	Comment noted. Comment noted. Comment noted. The technology will be appraised in line with its UK marketing authorisation. No change to the scope required
Additional comments on	AB Science	Significant results could be presented in the draft scope after introducing the study design	Comment noted.

Section	Consultees	Comments	Action
the draft scope.	Pfizer	No comments.	Comment noted.
	Sarcoma UK	Related NICE recommendations should include reference to 'Improving Outcomes for Patients with Sarcoma' published in 2006. It should be noted that page 77/78 contains recommendations which require the care of GIST patients in a non-sarcoma site specific MDT to consult with a sarcoma specific MDT, especially with regard to care plans and clinical trials. This does not routinely happen, to the dis-benefit of a proportion of patients. We are deeply concerned about the piecemeal way treatments for GIST are being appraised by NICE. The focus on individual technologies, one at a time, is not a recipe for identifying or valuing the benefits that patients can potentially achieve in this disease. A whole pathway view which takes account of a variety of technologies, made available according to individual need assessed and prescribed by a specialist clinician, is the only appropriate way forward if this Government's aim of improving outcomes is to be attained.	The Cancer Service Guidance 'Improving outcomes for people with sarcoma' has been added to the list of related guidance in the scope. The Centre of Clinical Practice at NICE undertakes clinical guidelines following the referral of a topic by the Department of Health. At present, no referral has been received for a clinical guideline for sarcoma.

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

Department of Health
Medicines and Healthcare products Regulatory Agency
Royal College of Nursing

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Add Independent Cancer Patient's Voice	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. Independent Cancer Patient's Voice has been added to the matrix of consultees and commentators under 'patient groups'.

2.	Add Association of Surgeons of Great Britain and Ireland	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. Association of Surgeons of Great Britain and Ireland has been added to the matrix of consultees and commentators under 'professional groups'.
3.	Add British Association of Surgical Oncology	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. British Association of Surgical Oncology has been added to the matrix of consultees and commentators under 'professional groups'.

4.	Add Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland has been added to the matrix of consultees and commentators under 'professional groups'.
5.	Add UK Health Forum	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. UK Health Forum has been added to the matrix of consultees and commentators under 'professional groups'.
6.	Remove County Durham and Darlington PCT Cluster	NICE Secretariat		Removed	This organisation has disbanded.
7.	Remove Calderdale, Kirlees and Wakefield PCT Cluster	NICE Secretariat		Removed	This organisation has disbanded.

8.	Add NHS Leeds South and East CCG	NICE Secretariat		Added	Our process requires the involvement of two CCGs. Therefore NHS Leeds South and East CCG is now included.
9.	NHS Telford and Wreckin CCG	NICE Secretariat		Added	Our process requires the involvement of two CCGs. Therefore NHS Telford and Wreckin CCG is now included.
10.	Add NHS England	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. NHS England has been added to the matrix of consultees and commentators under 'other groups.'
11.	Reclassify Public Health Wales NHS Trust as an associated public health group.	NICE Secretariat		Re-classified	This organisation has been re-classified as an 'associated public health group - commentator'.

12.	Health Research Authority	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. Health Research Authority has been added to the matrix of consultees and commentators under 'professional groups'.
13.	Add Public Health England	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. Health Research Authority has been added to the matrix of consultees and commentators under 'professional groups'.
14.	Remove Independent Age	NICE Secretariat		Removed	This organisation has been removed from the matrix at their own request.

15.	Add Ochre	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. Ochre has been added to the matrix of consultees and commentators under 'patient groups'