National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Imatinib for the adjuvant treatment of gastrointestinal stromal tumours (review of TA196)
Response to consultee and commentator comments on the draft scope

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	Novartis	The background information is correct but it should be noted that the figures quoted therein relate to GIST in general. Imatinib is indicated only for those patients at significant risk of tumour recurrence.	Comment noted. The background section gives a brief introduction to the disease and is accurate. The technology section states imatinib's relevant indication. No change to the scope required.
	Royal College of Pathologists	The first paragraph should include a statement that the specific mutation type of the GIST can help predict clinical response to imatinib. GIST mutation testing can therefore be used to help stratify patients for adjuvant imatinib therapy.	Comment noted. A short statement saying that tumour mutational status can be predictive of treatment response has been added to the background section of the scope.

Section	Consultees	Comments	Action
	Sarcoma UK	Broadly accurate. It may be worth noting that a percentage of patients present with metastatic or unresectable disease which responds to imatinib and thus makes surgery possible. Such patients usually continue on imatinib post surgery. They are not receiving adjuvant therapy as they are metastatic/unresectable patients.	Comment noted. The background section is intended to provide a brief introduction to the disease. Only adjuvant treatment with imatinib is being appraised so this group of patients is not directly relevant to this appraisal. No change to the scope required.
The technology/ intervention	Novartis	*In response to the question 'Is the description of the technology or technologies accurate?* Yes	Comment noted. No action required.
	Royal College of Pathologists	No comments	Comment noted. No action required.
	Sarcoma UK	Broadly accurate. It should be noted that various risk assessment methodologies have been used to determine patients at low/medium/high risk and that this work continues. The current scale in general use is that published by Miettinen & Lasota (USA). Genomic assessment of the medium risk group through the work of CINSARC (Chibon – France) indicates that this risk category may disappear in a later publication, with all patients being categorized as high or low risk. NICE must be aware that such work continues and must not recommend a specific risk assessment tool which may be quickly superseded in clinical practice.	Comment noted. The technology section directly quotes the relevant indication in the European marketing authorisation ('adjuvant treatment of adult patients who are at significant risk of relapse following resection of KIT (CD117)-positive GISTs'). This technology appraisal will appraise imatinib within its licensed indication. No change to the scope required.

Section	Consultees	Comments	Action
Population	Novartis	The Novartis submission will focus on adults who are *at high risk* (according to Miettinen criteria) of tumour relapse following resection of KIT (CD/117)-positive GIST Without treatment, five-year recurrence-free survival (RFS) in the high-risk subgroup is 20%. Insufficient subgroup data exist to consider the importance of mutational status analysis further to KIT and/or PDGFRA positivity with regards to imatinib efficacy.	Comments noted. The technology will be appraised within its licensed indication, which is for adults who are at 'significant' risk of relapse following resection of KIT (CD117)-positive GIST. No change to the scope required. Subgroup analyses by baseline risk of relapse and tumour genetic mutational status should be considered if evidence allows. No change to the scope required.
	Royal College of Pathologists	At least a third of GISTs lacking CD117 immunopositivity will harbour tyrosine kinase mutations that predict for sensitivity to imatinib. Therefore, the population should not be restricted to patients with CD117 positive GISTs and instead should include all GIST patients.	Comment noted. NICE can only issue guidance within the scope of a technology's UK marketing authorisation. Imatinib's marketing authorisation for the relevant indication states that tumours must be CD117+. No change to the scope required.

Section	Consultees	Comments	Action
	Sarcoma UK	The high risk category is the target group. Patients whose primary mutation is at D842V in PDGFRA do not respond to imatinib and should be excluded from this review. This may require genetic mutation analysis as standard of care.	Comment noted. The technology will be appraised within its licensed indication, which is for adults who are at 'significant' risk of relapse following resection of KIT (CD117)-positive GIST. No change to the scope required. Subgroup analyses by baseline risk of relapse and tumour genetic mutational status should be considered if evidence allows. No change to the scope required.
Comparators	Novartis	In the context of TA196, which does not recommend the use of imatinib in adjuvant GIST, the comparator would be no treatment. However, it should be noted that, since TA196 was published, survival data from the SSG trial have been released and adjuvant treatment has become standard of care for those patients at high-risk of recurrence. Its use is supported in this setting by both SMC advice in Scotland and CDF funding in England, along with national and international guidelines.	Comment noted. Adjuvant treatment with imatinib is the technology being appraised and is therefore classified as the intervention in this appraisal. The comparator is no treatment after surgery. No change to the scope required.
	Royal College of Pathologists	No comments	Comment noted. No action required.
	Sarcoma UK	The relevant comparator with adjuvant imatinib is the one used in the EORTC study – observation following surgery.	Comment noted. For clarity, the comparator in the scope has been amended to 'Observation after surgery (no adjuvant therapy)'.

Section	Consultees	Comments	Action
Outcomes	Novartis	Yes, all the outcome measures listed in the draft scope are relevant and will be included in our analysis	Comment noted. No action required.
	Royal College of Pathologists	No comments	Comment noted. No action required.
	Sarcoma UK	Understanding overall survival (OS) as an outcome measure presents challenges because of the successive therapies now available to patients. A patient relapsing following adjuvant imatinib will receive imatinib as first-line therapy. The study needs to be aware that patients on imatinib post-recurrence can continue on treatment for many years (currently there are patients at 12+ years). Physical decline due to the disease follows resistance to imatinib and later therapies are not as effective in offering control. Once imatinib resistance occurs interventions can include surgery, RFA, second- and third- line TKI therapies, and use of new radiotherapy technology. There is also an active research programme internationally and new therapies are in trials. The EORTC trial used the principle outcome of 'resistance to first TKI' attempting to identify a point in the pathway of disease which could not be distorted by later therapies and which is regarded as a determinant of survival. The SSG study reported recurrence free survival (RFS) as its primary outcome and OS as a secondary endpoint . All patients received imatinib therapy (a two-arm randomisation between 1 and 3 years). It reported an improvement in both RFS and OS for patients taking adjuvant therapy for 3 years over those who took it for one year. The ACOSOG study was placebo controlled and used recurrence-free survival as its principle outcome measure. We recognise the value of the OS endpoint but because of the clear benefit imatinib offers in first-line therapy we believe that rather than recurrence-free survival (taking the first recurrence as the endpoint) the endpoint adopted by EORTC (resistance to first TKI) should be considered as the secondary outcome measure for this Appraisal. It offers a fairer view of the benefits of adjuvant therapy because it records the most important prognostic development in the patient pathway.	Comments noted. Both overall survival and recurrence-free survival are outcomes listed in the scope. No change to the scope required.

Section	Consultees	Comments	Action
	Southampton Health Technology Assessments Centre	Long term data should be included where available since the last appraisal.	Comment noted. The manufacturer should provide all relevant evidence in its submission. No change to the scope required.
Economic analysis	Novartis	The analysis will follow the NICE reference case. An updated version of the model submitted for TA196 will be used. Lifetime horizon will be considered.	Comment noted. No action required.
	Royal College of Pathologists	The stratification of GIST patients for adjuvant imatinib therapy based on the tumour mutation type will impact directly on the clinical aspects and economics of this technology. This technology appraisal should therefore formally assess this role for GIST mutation testing and therefore include the cost of mutation testing in its economic analysis.	Comment noted. The NICE 'Guide to the methods of technology appraisal 2013' notes that if a diagnostic test to establish the presence or absence of this biomarker is carried out solely to support the treatment decision for the specific technology, the associated costs of the diagnostic test should be incorporated into the assessments of clinical and cost effectiveness. A sensitivity analysis should be provided without the cost of the diagnostic test. The scope has been amended to reflect this.
	Sarcoma UK	None	Comment noted. No action required.

Section	Consultees	Comments	Action
	Southampton Health Technology Assessments Centre	The previous ERG made critical comments on the original economic model so the current ERG would expect the manufacturers to develop/change the model for the current appraisal. Also, there have been recent cost effectiveness models published in the literature which will need consideration.	Comment noted. No change to the scope required.
Equality and Diversity	Novartis	The draft scope does not appear to contradict the NICE commitment to equality.	Comment noted. No action required.
	Royal College of Pathologists	No comments	Comment noted. No action required.
	Sarcoma UK	We know of no relevant factors	Comment noted. No action required.
Innovation	Royal College of Pathologists	No comments	Comment noted. No action required.
	Sarcoma UK	Adjuvant imatinib is pointing to a significant improvement in survival with a high quality of life for the additional years for those patients at the highest risk of a relapse. This can be seen as a step-change clinically. Its value has been recognised worldwide with the ready adoption of the adjuvant approach. It should be noted that genetic mutation testing helps inform clinicians on the appropriateness of treatments in the patient pathway, especially for those who do not have the most common KIT exon11 primary mutation. This is not routine in all NHS centres treating GIST. Such testing should be routine following surgery/biopsy to ensure that patients can be suitably matched to available therapies as the experience and knowledge of those therapies grows.	Comments noted. The manufacturer will be able to include its argument for the innovative nature of the technology in its submission. No change to the scope required.

Section	Consultees	Comments	Action
Other considerations	Novartis	Insufficient data are available to allow an assessment of cost-effectiveness for sub-groups according to mutational status. As stated above, the Novartis submission will focus on the high-risk sub-group, since this is the patient group who have the greatest capacity to benefit from treatment. The economic analysis will consider only these patients.	Comments noted. Subgroup analyses by baseline risk of relapse and tumour genetic mutational status should be considered if evidence allows. No change to the scope required. The technology will be appraised within its licensed indication, which is for adults who are at 'significant' risk of relapse following resection of KIT (CD117)-positive GIST. No change to the scope required.
	Royal College of Pathologists	See 'Economic analysis' comments	Comment noted. No action required.
	Sarcoma UK	None	Comment noted. No action required.
Questions for consultation	Royal College of Pathologists	No comments	Comment noted. No action required.
	Sarcoma UK	'Other Considerations' are appropriate. Imatinib is taken continuously so the concept of treatment cycles is artificial.	Comment noted. No action required.

Section	Consultees	Comments	Action
Additional comments on the draft scope.	Novartis	In the main, data will be drawn from the publications and CSRs for the ACOSOG and SSG studies. Where necessary, these will be supplemented using data identified in the systematic review. An indirect comparison, using patient-level data, has been conducted to allow the three-year treatment duration to be considered in relation to no adjuvant treatment.	Comment noted. No action required.
	Royal College of Pathologists	None	Comment noted. No action required.
	Royal College of Physicians	Our experts have no objection to the draft scope. We welcome the review of adjuvant imatinib and are enthusiastic to support this.	Comment noted. No action required.

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

Healthcare Improvement Scotland
Royal College of Nursing

NATIONAL INSTITUTE FOR HEALTH CARE EXCELLENCE

Single Technology Appraisal (STA)

Imatinib for the adjuvant treatment of gastrointestinal stromal tumours (review of TA196)

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 Association of Clinical Pathologists	Royal College of Pathologists		Added	This organisation has an area of interest directly related to this appraisal and meets the selection criteria to participate in this appraisal. Association of Clinical Pathologists has been added to the matrix of consultees and commentators under 'professional groups.'

2.	Add British Sarcoma Group	Sarcoma UK		Added	This organisation has an area of interest directly related to this appraisal and meets the selection criteria to participate in this appraisal. British Sarcoma Group has been added to the matrix of consultees and commentators under 'professional groups.'