Professional organisation statement template

Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours (part review of Technology Appraisal No. 86)

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:

Submitted by [redacted], [redacted] on behalf of:

Name of your organisation

NCRI/RCP/RCR/ACP/JCCO

Comments coordinated by [redacted] and [redacted]

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? √
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? √
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The tyrosine kinase inhibitor imatinib is the treatment of choice for unresectable or metastatic gastrointestinal stromal tumour (GIST) and is generally given at a dose of 400 mg daily. However, the European Organization for Research & Treatment of Cancer (EORTC) Soft Tissue & Bone Sarcoma Group (STBSG) initially initiated a phase I trial that explored the dose range 400 to 1000 mg daily. This study demonstrated a high level of efficacy and established 800 mg daily (400 mg b.d) as the maximum tolerated dose (MTD)[1]. Subsequent parallel studies were performed in Europe, with Australasia, (EORTC trial 62005) and in North America (study S0033) comparing the standard dose of 400 mg daily with the MTD dose from the EORTC study of 800 mg. These trials were completed rapidly, EORTC 62005 recruited 946 patients between February 2001 and February 2002, trial, S0033 recruited 746 patients in nine months[2]. Both studies reported that the two doses produced similar response rates and recommended that the starting dose of imatinib should be 400 mg daily. However, the EORTC study reported that progression-free survival was superior for the 800 mg dose[3].

Cross-over from 400 mg to 800 mg

Data emerged from both the 62005 and S0033 studies suggesting that a higher dose of imatinib could be beneficial for some patients who did not respond optimally to 400 mg daily. Both studies allowed patients randomised to 400 mg to receive 800 mg on disease progression, or failure to respond. Trial 62005 reported that 55% of patients who progressed on 400 mg crossed over the higher dose, of whom 29% had a response or disease stabilisation, albeit the objective remission rate was low and median time on drug after cross-over was only 81 days[4]. Nevertheless 18% were still alive and progression-free at a year, indicating significant benefit. In the North American trial a similar proportion of patients, 33%, had a remission or stable disease after cross-over[2].

The influence of *KIT* and *PDGFRA* genotype

GISTs are known to be caused by activating mutations of genes encoding for one of two cell surface receptors, KIT and PDGFRA. In the last few years an enormous amount has been learnt concerning the impact of different gene mutation types on the intrinsic aggressiveness of GIST and its response to tyrosine kinase inhibitors. While the majority of mutations are in *KIT*, Heinrich *et al* reported that mutations in *PDGRA* were also present in a minority of GISTs, and that these resulted in the same pattern of downstream signalling as *KIT* mutations as defined by protein phosphorylation[5], but not according to gene expression[6]. In addition, significant differences in responsiveness to imatinib were observed according to which *KIT* or *PDGFRA* exons were mutated, or indeed if no mutations were detected, with best responses seen with patients with KIT exon 11 gene mutations. It was noted that malignant behaviour correlates with tumour size and mitotic index[7]. It is also recognised that tumour site is important, in that gastric GISTs fare much better than those arising in the small intestine[8]. This may be partly due to the fact that *KIT* exon 9 mutations, associated with a relatively poorer response to imatinib[9], are commoner in the small intestine, and conversely, *PDGFRA* mutations, apparently associated with a more indolent growth pattern are not seen in the small intestine[10, 11].

Impact of genotype on choice of imatinib dose

A mutational analysis performed on 377 of the patients recruited into the EORTC study 62005 confirmed the previously reported adverse impact of *KIT* exon 9 mutation on response and response duration with imatinib, increasing the relative risk of progression by 171% ($p<0.0001$) and relative risk of death by 190% ($p<0.0001$) compared with exon 11[12]. Patients with no detectable mutations also fared worse, with an increased risk of progression of 108% ($p<0.0001$) and death of 76% ($p=0.028$). There was also a major difference in the exon 9 group of patients in relation to the dose of imatinib used. Exon 9 patients treated with 800 mg imatinib daily had a highly significantly improved progression free survival (PFS) ($p=0.0013$), compared with 400 mg, albeit median PFS for exon 9 patients was still worse than for those with exon 11 mutations. No detectable difference was observed according to dose in the patients with *KIT* exon 11 mutations. This fact suggests that the benefit in the group as a whole reported by Verweij *et al*[3] with regard to an initial treatment dose of imatinib 800 mg was largely due to the exon 9 patients. A subsequent meta-analysis of the combined data from EORTC study 62005 and S0033 was presented at

ASCO 2007[13]. This showed that in the study population of 1640 patients as a whole the benefit for the higher dose in *KIT* exon 9 mutant disease was retained with a hazard ratio of 0.58 (p=0.017) (Table 1.). No survival advantage was reported.

Table 1.

		Number	Median estimate (years)		Hazard Ratio	*P*-value
			o.d.	b.i.d.		
PFS	All patients	1640	1.58	1.95	0.89	0.041
	Europe-Australia	946	1.74	2.02	0.89	0.12
	US-Canada	694	1.46	1.64	0.89	0.18
OS	All patients	1640	4.08	4.05	1.00	0.97
PFS	*KIT* exon 9 mutant	91	0.5	1.59	0.58	0.017
	Europe-Australia	59	0.35	1.62	0.43	0.0023
	US-Canada	32	0.78	1.4	0.99	0.97

Adapted from: van Glabbeke M, OwzarK., Rankin C., Simes J., Crowley J., GIST Meta-analysis Group (MetaGIST). Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumor (GIST): A meta-analysis based on 1,640 patients. J Clin Oncol 2007; 25: 18s abstract 10004.
o.d. once daily = 400 mg, b.i.d. twice daily = 800 mg

The 800 mg imatinib dose is licensed, but is not endorsed by existing NICE guidance from 2004. This has inevitably resulted in substantial geographical variability in its use in the UK, and in the accessibility of patients to higher doses of the drug. It is recommended in the NICE IOG on people with sarcoma that patients with GIST should be managed in the context of a multidisciplinary team with expertise in the disease, i.e. only by experienced specialists, and hence this should apply to the supervision of imatinib therapy. Clinical guidelines published both by the National Cancer Coordinating Network (NCCN) in the USA[14] and the European Society of Medical Oncology (ESMO)[15] both recommend the use of imatinib at a dose of 800 mg daily for patients with progressive disease on 400 mg daily and particularly in the case of *KIT* exon 9 mutant disease, such that the use of imatinib 800 mg in these situations is considered standard of care in both USA and Europe.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements

for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The overall median duration of progression-free survival of patients with advanced GIST on imatinib is in the region of two years[3]. A number of mechanisms for acquired resistance have been identified, of which the commonest appears to be the acquisition of secondary mutations in *KIT* or *PDGFRA* that confer resistance, others being gene amplification leading to target over-expression, activation of alternative pathways, with loss of KIT expression and so-called "functional resistance", which is not well understood but may perhaps reflect changes in the expression of cellular transport proteins[9]. The clonal evolution of acquired resistance may present with subtle nodular changes in the density of tumours on CT, which on excision are likely to contain secondary mutations, which may be polyclonal[16]. Acquired mutations are, not surprisingly, more frequently observed after prolonged exposure to imatinib, i.e. in initially responsive exon 11 *KIT* mutant disease, than in exon 9 mutant patients, and also generally associated with very high levels of resistance *in vitro*[17]. Some of these mutations also confer resistance to sunitinib, whereas others do not, hence the value of this agent in the second line treatment of imatinib-refractory disease.

Current guidelines [14, 15] recommend that imatinib be continued in patients who are experiencing clinical benefit, even if their disease is progressing radiologically. This may appear counterintuitive but reflects the frequent clinical observation that patients may experience acute deterioration of symptoms and accelerated tumour growth on withdrawal of imatinib. There are many reasons why this might occur: firstly, only a percentage of tumour cells in a given tumour are thought to have acquired resistance, the remainder still being sensitive to imatinib; secondly, owing to the phenomenon of quiescence, on withdrawal of imatinib the sensitive cells that had been lying dormant rapidly re-enter the cell cycle and begin to proliferate (a tumour flare effect); thirdly, one of the effects of imatinib is to upregulate circulating growth factors, such as stem cell factor – the natural ligand for KIT, which may stimulate tumour growth in the absence of inhibitor. Thus, there are several reasons the justifiy the continuation of imatinib after radiological disease progression, although, if imatinib is to be continued in this context, it does not necessarily have to be given at the higher, 800 mg dose.

Although patients starting therapy with imatinib 800 mg daily experience substantially more toxicity than those starting at 400 mg, the same is not true of patients who have been receiving the lower dose for some time and then have their dose escalated, as the side effects have been shown to lessen with time[18]. Hence, toxicity of the higher dose is not expected to be a significant problem, and in most patients the side effects of imatinib 800 mg compare favourably with those of sunitinib.

Currently there are no data to indicate whether switching to a higher dose of imatinib or changing to sunitinib is the more effective strategy in the initial management of patients who are progressing on imatinib after an initial response or who are early progressors. There are some data to suggest that patients progressing early may have the unfavourable exon 9 mutation, in which case they are very likely to benefit from a higher dose. If a secondary mutation has occurred in a patient with a primary imatinib sensitive mutation then it is likely that a higher dose will not work. This will be apparent very quickly necessitating a switch to sunitinib. However, the fact that about a third of patients appear to derive significant benefit from dose escalation[4], many more than could be explained by exon 9 mutations, which are not so frequent (present in about 8 – 15%), suggests that other mechanisms of resistance must apply.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

One issue that is unclear at present is the role of therapeutic blood level monitoring. Imatinib blood level testing has become quite routine in the management of chronic myeloid leukaemia (CML). There are limited data from the US randomised phase II trial in GIST that, as in the case of CML, failure to maintain a similar minimum effective imatinib blood level of 1100 ng/ml may also define a population of patients with GIST who are less likely to respond and more likely to progress early[19]. This suggests that some of the benefit of dose escalation could be explained by pharmacokinetic variation between patients. Although the Demetri study did not confirm it, there are limited data to suggest that the clearance of imatinib may increase with time in patients with GIST[20]. Prospective pharmacokinetic studies in patients progressing on standard dose imatinib and crossing over to the higher dose would be valuable.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

No implementation or resource issues in terms of staff training are anticipated.

References

1. van Oosterom AT, Judson I, Verweij J et al. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. Lancet 2001; 358: 1421-1423.
2. Blanke CD, Rankin C, Demetri GD et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. J Clin Oncol 2008; 26: 626-632.
3. Verweij J, Casali PG, Zalcberg J et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet 2004; 364: 1127-1134.
4. Zalcberg JR, Verweij J, Casali PG et al. Outcome of patients with advanced gastro-intestinal stromal tumours crossing over to a daily imatinib dose of 800 mg after progression on 400 mg. Eur J Cancer 2005; 41: 1751-1757.
5. Heinrich MC, Corless CL, Duensing A et al. PDGFRA activating mutations in gastrointestinal stromal tumors. Science 2003; 299: 708-710.
6. Subramanian S, West RB, Corless CL et al. Gastrointestinal stromal tumors (GISTs) with KIT and PDGFRA mutations have distinct gene expression profiles. Oncogene 2004; 23: 7780-7790.
7. Fletcher CD, Berman JJ, Corless C et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol 2002; 33: 459-465.
8. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006; 23: 70-83.
9. Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. J Clin Oncol 2004; 22: 3813-3825.
10. Miettinen M, Makhlouf H, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. Am J Surg Pathol 2006; 30: 477-489.
11. Lasota J, Miettinen M. KIT and PDGFRA mutations in gastrointestinal stromal tumors (GISTs). Semin Diagn Pathol 2006; 23: 91-102.

12. Debiec-Rychter M, Sciot R, Le Cesne A et al. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. Eur J Cancer 2006; 42: 1093-1103.
13. van Glabbeke M, OwzarK., Rankin C., Simes J., Crowley J., GIST Meta-analysis Group (MetaGIST). Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumor (GIST): A meta-analysis based on 1,640 patients. J Clin Oncol 2007; 25: abstract 10004.
14. Demetri GD, Benjamin RS, Blanke CD et al. NCCN Task Force report: management of patients with gastrointestinal stromal tumor (GIST)--update of the NCCN clinical practice guidelines. J Natl Compr Canc Netw 2007; 5 Suppl 2: S1-29; quiz S30.
15. Blay JY, Bonvalot S, Casali P et al. Consensus meeting for the management of gastrointestinal stromal tumors. Report of the GIST Consensus Conference of 20-21 March 2004, under the auspices of ESMO. Ann Oncol 2005; 16: 566-578.
16. Desai J, Shankar S, Heinrich MC et al. Clonal evolution of resistance to imatinib in patients with metastatic gastrointestinal stromal tumors. Clin Cancer Res 2007; 13: 5398-5405.
17. Heinrich MC, Maki R.G., Corless C.L., Antonescu C.R., Fletcher J.A., Fletcher C.D., Huang X., Baum C.M., Demetri G.D. Sunitinib (SU) response in imatinib-resistant (IM-R) GIST correleates with *KIT* and *PDGFRA* mutation status. J Clin Oncol 2006; 24: abstract 9502.
18. Verweij J, van Oosterom A, Blay JY et al. Imatinib mesylate (STI-571 Glivec, Gleevec) is an active agent for gastrointestinal stromal tumours, but does not yield responses in other soft-tissue sarcomas that are unselected for a molecular target. Results from an EORTC Soft Tissue and Bone Sarcoma Group phase II study. Eur J Cancer 2003; 39: 2006-2011.
19. Demetri GD, Wang Y, Wehrle E et al. Imatinib plasma levels are correlated with clinical benefit in patients with unresectable/metastatic gastrointestinal stromal tumors. J Clin Oncol 2009; 27: 3141-3147.
20. Judson I, Ma P, Peng B et al. Imatinib pharmacokinetics in patients with gastrointestinal stromal tumour: a retrospective population pharmacokinetic study over time. EORTC Soft Tissue and Bone Sarcoma Group. Cancer Chemother Pharmacol 2005; 55: 379-386.