**National Institute for Health and Clinical Excellence**
**Health Technology Appraisal**

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

**Comment 1: the draft scope**

| Section | Consultees | Comments | Action |
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| Background information | **GIST Support UK, Rarer Cancers Forum, Sarcoma UK Submitted on behalf of the responders by SarcomaUK** | The results from Study B2222 show clinical benefit from 400mgs imatinib in 84% of patients with metastatic or unresectable GIST. Initial resistance to imatinib is therefore 16%, not 30-50%. The higher figure is for resistance after 6 months. Many of those developing early resistance are patients whose c-Kit mutation is not at Exon 11. | Comment noted. Scope amended accordingly. |
| | | Patients who respond to imatinib in first-line have a median time to developing resistance to the drug at about 2 years. The strategy adopted by international consensus at this stage is to consider escalating the dose to 600mg or 800mg/day. | Comment noted. The appraisal will consider the clinical and cost-effectiveness of imatinib dose escalating. |
| | | However for one group of patients, those with an Exon 9 mutation in c-Kit, there is now good evidence that escalating to a dose of 800mg/d during the first few months of treatment delays the development of resistance. This may apply to the Exon 11 group too as it is apparent that some patients receiving 800mg day (regardless of mutation status) achieve long term disease free survival (>7 years). This is a small group of patients who were randomised to 800mg per day in the Phase 3 trials starting in 2001. | Comment noted. If the evidence allows, subgroup analysis by mutational type will be considered and any costs associated with subtyping should be included in the economic analysis. See under 'other considerations' in the final scope. |

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| Background information (continued) | **GIST Support UK, Rarer Cancers Forum, Sarcoma UK Submitted on behalf of the responders by SarcomaUK** | Patients who are withdrawn from imatinib on developing resistance, and progression of disease, have a poor prognosis – untreated less than 2 years. There is also evidence from a French RCT that disease accelerates on withdrawal. Patients who remain on a maintenance dose of imatinib have a median overall survival of 5 years.<br>The complexity of addressing these issues is such that in few of the above instances is the number of patients sufficiently large to be statistically significant. This is due to the small numbers of patients overall. An RCT to test hypotheses based on the above issues is not usually possible for both practical and ethical reasons. | Comment noted. The appraisal will consider the clinical and cost-effectiveness of imatinib dose escalating. Also, a NICE technology appraisal of sunitinib for the treatment of people with unresectable and/or metastatic malignant GIST is currently ongoing. |
| | | We believe this rarity should be clearly stated in the scope. It should be acknowledged by NICE that the well developed scientific understanding of issues of this kind will be considered in the Appraisal with status equal to that of peer reviewed publications because of the rarity issue. | Comment noted. No action required. |
| | | The NICE appraisal of sunitinib is almost complete, with approval of sunitinib for patients with ECOG status 0 and 1. (An appeal is pending for the inclusion of ECOG status 2.) | Comment noted. NICE technology appraisal of sunitinib for the treatment of people with unresectable and/or metastatic malignant GIST is currently ongoing. |
| | | There is also a trial open, comparing 800mgs of imatinib with sunitinib for patients with progression on 400mgs of imatinib, and a trial about to open comparing imatinib and nilotinib for first line treatment. | Comment noted. No action required. |
| | **Pfizer Ltd** | The wording of the background information is appropriate. | Comment noted. No action required. |

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| Background information (continued) | **National Cancer Research Institute (NCRI), Royal College of Physicians (RCP), Royal College of Radiologists (RCR), Association of Cancer Physicians (ACP), Joint Council of Clinical Oncology (JCCO)** | The nature of the problem is well described, i.e. GIST progressing after a period of time on imatinib 400 mg daily. However, on page 2 of the draft scope it is stated that a STA of sunitinib in this context is ongoing, whereas a decision has been made that sunitinib is an effective agent with the ability to prolong disease-free and overall survival. | Comment noted. The scope was amended to express that a Final Appraisal determination (FAD) for the NICE technology appraisal of sunitinib for the treatment of people with unresectable and/or metastatic malignant GIST has been issued. |
| | **Health Services Research Unit/Health Economics Research unit, University of Aberdeen** | No comments on this section. | Comment noted. No action required. |

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| The technology/ intervention | **GIST Support UK, Rarer Cancers Forum, Sarcoma UK Submitted on behalf of the responders by SarcomaUK** | Yes | Comment noted. No action required. |
| | **Novartis Pharmaceuticals UK Limited** | It is appropriate to focus the review on patients who have progressed on a 400 mg/day dose of imatinib Guidance regarding patients who continue to respond on 400 mg/day is adequately addressed in TA86.<br>In clinical practice, it is unlikely that any patient who has progressed on imatinib 400 mg will continue on imatinib at the same dose since there are other treatment options available. The intervention should therefore be only "Imatinib at escalated doses of 600 mg/day or 800 mg/day" | Comment noted. Scope amended accordingly. |
| | **NCRI/RCP/RCR/ACP/JCCO** | Yes | Comment noted. No action required. |
| | **Health Services Research Unit/Health Economics Research unit, University of Aberdeen** | No comments on this section | Comment noted. No action required. |
| Licensing Issues (only for manufacturers to complete) | **Novartis Pharmaceuticals UK Limited** | Licensed | Comment noted. No action required. |

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| Population | **GIST Support UK, Rarer Cancers Forum, Sarcoma UK Submitted on behalf of the responders by SarcomaUK** | It is now known that there are different mutations which cause GIST and patients with different mutations respond differently to imatinib. Mutations also evolve during treatment.<br>It is as inappropriate to disregard the GIST mutation sub-groups as it would be inappropriate to disregard hormone positive sub-groups in breast cancer. Failure to do so will be open discrimination against this rare cancer group.<br>This issue is most significant clinically with the difference between Exon 11 (good initial response at 400mg/d) and Exon 9 (best responses at 800mg/d). | Comment noted. If the evidence allows, subgroup analysis by mutational type will be considered and any costs associated with subtyping should be included in the economic analysis. See under 'other considerations' in the final scope. |
| | **Novartis Pharmaceuticals UK Limited** | The population is defined appropriately.<br>However, dose escalation is not considered to be an option for imatinib-intolerant patients. | Comment noted. Sunitinib is included as a comparator. |
| | **NCRI/RCP/RCR/ACP/JCCO** | At the time of the first STA on imatinib for the treatment of GIST it was already known that there was a progression-free survival advantage for imaitnib 800 mg daily compared with 400 mg, albeit the full paper had not been published. It is now well established that patients with exon 9 mutations in KIT experience superior progression-free survival on imatinib 800 mg daily and are more likely to respond to the higher dose. The combined data from 1640 patients treated in both the European and North American trials have been used to confirm this finding. These patients were also more likely to benefit from sunitinib in the registration trial but this was apparently because these patients had progressed quickly on imatinib and were much less likely to have developed secondary mutations capable of conferring resistance both to imatinib and sunitinib.<br>The other group of patients requiring specific attention are those with no identifiable mutations in KIT or PDGFRA, i.e. so-called "wild-type" disease. This most commonly occurs in young women, often presenting with profound anaemia and multifocal disease arising initially in the stomach. Limited clinical experience and laboratory data appear to demonstrate that sunitinib is a superior agent compared with imatinib in this patient population. | Comment noted. If the evidence allows, subgroup analysis by mutational type will be considered and any costs associated with subtyping should be included in the economic analysis. See under 'other considerations' in the final scope. |

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| Population (continued) | **Health Services Research Unit/Health Economics Research unit, University of Aberdeen** | Population is appropriate, no other comments on this section | Comment noted. No action required. |
| Comparators | **GIST Support UK, Rarer Cancers Forum, Sarcoma UK Submitted on behalf of the responders by SarcomaUK** | Yes, with one reservation. Sunitinib is generally offered as a third-line therapy (despite its second-line licensed indication). It should be noted in any comparison that there is a loss of both performance status and health utility with each additional therapeutic line. | Comment noted. Scope amended accordingly. |
| | **Novartis Pharmaceuticals UK Limited** | In clinical practice, all patients who progress on imatinib 400mg/day would be offered a clinical alternative such as an escalated dose of imatinib to 600mg or 800mg/day. After failure of dose escalation, sunitinib becomes the next treatment option*.<br>Since imatinib dose escalation to 600 mg or 800mg/day is the first option for patients who fail on 400 mg imatinib and treatment with sunitinib is the second line option, the continued dose (400 mg) and sunitinib are not valid comparators.<br>*As per the STA FAD of "Sunitinib for the treatment of GISTSs after failure of imatinib treatment due to resistance or intolerance". In accordance with the pivotal RCT, sunitinib was positioned in the patient pathway after imatinib dose escalation. | Comment noted. Scope amended accordingly. |
| | **NCRI/RCP/RCR/ACP/JCCO** | The biggest problem with attempting to compare higher dose imatinib with sunitinib in GIST that is refractory to imatinib 400 mg daily is the lack of direct comparative data. A clinical trial is underway to address this. However, what is often difficult to determine from such studies is the survival advantage to be derived from sequential effective treatments. | Comment noted. No action required. |

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| Comparators (continued) | **Health Services Research Unit/Health Economics Research unit, University of Aberdeen** | One of our clinical advisers commented that the key comparison for clinicians will be dose escalation of Imatinib versus Sunitinib following first line failure on lower dose Imatinib. Appropriate that best supportive care is also included as a comparator. There are no other comparators that should be included. | Comment noted. Scope amended accordingly. |
| Outcomes | **GIST Support UK, Rarer Cancers Forum, Sarcoma UK Submitted on behalf of the responders by SarcomaUK** | Yes | Comment noted. No action required. |
| | **Novartis Pharmaceuticals UK Limited** | The outcome measures listed are appropriate. In addition, we would recommend including<br>- clinical benefit (stable disease or overall response), measured within 12 weeks of starting new treatment | Comment noted. Overall response has been added as an outcome. |
| | **Pfizer Ltd** | All outcomes relevant to this condition are included. | Comment noted. No action required. |
| | **NCRI/RCP/RCR/ACP/JCCO** | Yes | Comment noted. No action required. |
| | **Health Services Research Unit/Health Economics Research unit, University of Aberdeen** | Outcomes are appropriate, no other comments on this section | Comment noted. No action required. |

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| Economic analysis | **GIST Support UK, Rarer Cancers Forum, Sarcoma UK Submitted on behalf of the responders by SarcomaUK** | It would be very useful to have an interim report on the trial comparing 800mgs imatinib with sunitinib before this appraisal, if one were available.<br>We are concerned at the general absence of statistically significant QoL data in rare diseases. Our own evidence is that patients on an escalated dose of imatinib may have a EQ-5D utility state ranging from .238 to 1.0 This range is so wide that finding an acceptable average will be problematic, but our sample is small. The data also indicates a differential with sunitinib, but as sunitinib is usually a third-line therapy this comparator is not reliable. | Comment noted. No action required. |
| | **NCRI/RCP/RCR /ACP/JCCO** | The time horizon is certainly important. In the first phase II study to be conducted, which commenced in 2000, survival data indicate median survival for patients with advanced metastatic or unresectable GIST treated with imatinib 400 mg daily of approximately 5 years. Patients starting treatment more recently may well have a better survival. | Comment noted. No action required. |
| | **Health Services Research Unit/Health Economics Research unit, University of Aberdeen** | No comments on this section | Comment noted. No action required. |
| Other considerations | **GIST Support UK, Rarer Cancers Forum, Sarcoma UK Submitted on behalf of the responders by SarcomaUK** | The question of the role of mutational analysis and the benefit which can be brought to both patients and the NHS by undertaking this analysis with all new GIST patients should be considered. The cost of this is small compared with the cost of the treatments.<br>The principle of ensuring that patients have both an appropriate and effective dose for their individual disease is one which is espoused in government policy. | Comment noted. If the evidence allows, subgroup analysis by mutational type will be considered and any costs associated with subtyping should be included in the economic analysis. See under 'other considerations' in the final scope. |

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| Other considerations (continued) | **NCRI/RCP/RCR /ACP/JCCO** | In addition to the obvious importance of mutational analysis in determining the most appropriate initial therapy, another important consideration is pharmacokinetic data. Preliminary results from one early imatinib trial demonstrate that patients with low blood levels are less likely to obtain a remission and have a shorter duration of disease control. It is possible, although as yet unproven, that some of the benefit of higher doses of imatinib is to achieve adequate blood levels, in addition to the effect on exon 9 KIT mutant disease. | Comment noted. If the evidence allows, subgroup analysis by mutational type will be considered and any costs associated with subtyping should be included in the economic analysis. See under 'other considerations' in the final scope. |
| | **Health Services Research Unit/Health Economics Research unit, University of Aberdeen** | One of our clinical advisers has stated that there will be a number of clinical issues for this appraisal that will require care, for example definition of progression, since it is recognised that there can be difficulties in assessing GIST progression using the conventional means of CT scanning unless performed by sufficiently experienced operators. | Comment noted. No action required. |
| Additional comments on the draft scope | **GIST Support UK, Rarer Cancers Forum, Sarcoma UK Submitted on behalf of the responders by SarcomaUK** | Only that it is long overdue! We know that clinical practise is frequently not in line with the current approval because research and clinical experience has shown the need for the use of 800mg/d of imatinib in some patients (and reduction of the 400mg dose in others.) The use of imatinib as a maintenance therapy after progression is also a valid life-extending treatment. This situation should now be formalised.<br>We are concerned that this appraisal is to be an MTA. Although TA86 was an MTA this was prior to the introduction of the STA. The timetable of an MTA is inevitably longer than an STA and we believe that in this indication, with a single manufacturer and a single therapy, the STA process is appropriate. NICE should not be bound by its prior practice and should be ready to adapt in the interest of timeliness, recognising the intent stated in the Cancer Reform Strategy. | Comment noted. The appraisal will consider the clinical and cost-effectiveness of imatinib dose escalating. The MTA process is appropriate for complex appraisals involving single technologies. |

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| Additional comments on the draft scope (continued) | **NCRI/RCP/RCR /ACP/JCCO** | NICE's recommendations are denying 10% of GIST patients valuable treatment.<br>[redacted] and [redacted] were the two RCPath reviewers that raised this point when NICE first assessed imatinib therapy for GISTs some five years ago and yet it seems that there is no consideration for change. Further, we now have markers that are just as useful, if not better, than CD117, notably DOG-1, and these should be included in the scope as these markers are more sensitive than CD117 for detecting GISTs.<br>When NICE first assessed this, the panel consisted of about 35 people, including two or three GPs and a few financial consultants, but not a single pathologist was on the panel. Perhaps this accounts for why one of the most crucial aspects of this whole scenario, getting the diagnosis right, is less than satisfactory. | Comment noted. The appraisal is looking at the clinical and cost-effectiveness of imatinib. The diagnosis of GIST is a separate issue. The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. |
| | **Pfizer Ltd** | NICE may wish consider subgroups based upon mutational status, as a review by Ian Judson (Current Opinion in Oncology 2008, 20:433-437) of phase III data and subsequent meta-analyses suggests that the sub-group of patiens with exon 9 mutations may respond better to 800mg imatinib | Comment noted. If the evidence allows, subgroup analysis by mutational type will be considered and any costs associated with subtyping should be included in the economic analysis. See under 'other considerations' in the final scope. |

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

1. **The Department of Health**
2. **NHS Quality Improvement Scotland**
3. **National Public Health Service for Wales**
4. **RICE – The Research Institute for the Care of Older People**
5. **The Royal Pharmaceutical Society of Great Britain**
6. **The Institute of Cancer Research**