# 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 guidance 86)

## Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

**Definitions:**

**Consultees –** Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

**Clinical specialists and patient experts** – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

**Commentators –** Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

**Public –** Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

## Comments received from consultees

| Consultee | Comment | Response |
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| **Novartis Pharmaceuticals** | 1. Summary<br><br>As Novartis has consistently highlighted in all the previous correspondence regarding this appraisal, clinical practice has shown that imatinib dose escalation is an effective treatment option which provides benefits to patients whose disease has progressed on imatinib 400 mg. Indeed, the UK National GIST Guidelines recommend dose escalating prior to switching to the only other licensed treatment option for these patients. However, because there are no new data from clinical trials, Novartis believes that there is insufficient evidence to justify the issuing of new guidance on recommendation 1.4 of TA86 in line with the NICE review process and therefore that the most appropriate action is to issue a recommendation reminder. Should NICE go ahead with issuing new guidance, this guidance should include an option stating that those already on doses of imatinib higher than 400 mg daily should continue until they and their clinicians consider it appropriate to stop. | Comment noted. The Committee noted that the UK National GIST guidelines contained the same evidence as was identified for this appraisal by the Assessment Group and the manufacturer, and that the development of the guideline had been sponsored by the manufacturer of imatinib. The Committee was aware that the UK GIST guideline did not consider the cost effectiveness of any treatments and therefore the recommendations in this appraisal would likely be different from the guideline (see FAD section 4.3.5).<br><br>The Committee concluded that the current available evidence does not justify a positive recommendation for the use of imatinib at increased doses of 600 mg/day and 800 mg/day as an appropriate use of NHS resources for the treatment of people with unresectable and/or metastatic GISTs whose disease has progressed on treatment with 400 mg/day imatinib (see FAD 4.3.20). |
| **Novartis Pharmaceuticals** | 2. Review process<br>According to section 6 of the guide to multiple technology appraisal process (October, 2009), a review of guidance is warranted only if there is sufficient evidence to change the current decision. Section 6.6 of the guide specifically suggests the following options if the guidance does not require updating:<br>• The guidance is valid and does not require an update because the evidence base is not likely to change substantially. It is therefore designated as static guidance.<br>• Defer the decision on if and how to update the published guidance to a future date.<br>• Incorporate the published guidance into a clinical guideline and withdraw the appraisal when the guideline is published.<br>As we have consistently highlighted in our previous submissions, there is no basis within the review process to justify the production of new guidance on imatinib dose escalation because the evidence base has not changed since the publication of TA86 in 2004. Section 4.3.3 of the ACD also concludes that there is a paucity of robust data available to demonstrate the effectiveness of increased doses of | Comment noted. The Committee noted that consultees had requested the review based on the belief that a large body of clinical evidence about imatinib had been published since 2004. In addition, the Committee was also reminded that, at the time of the review proposal, the manufacturer of imatinib was seeking a licence extension for 800 mg/day imatinib for the treatment of unresectable and/or metastatic GIST and supported the view that the review should go ahead. By contrast, during the Committee meeting, the Committee heard from the manufacturer that no new evidence on the effectiveness of increased doses of imatinib after disease progression on 400 mg/day imatinib has emerged since NICE technology appraisal guidance 86 was published in 2004. The Committee noted that this appraisal is a part review of 'Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours' (NICE technology appraisal guidance 86), and the scope was to review recommendation 1.4 only, about whether the dose of imatinib should be increased following disease progression on |

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>imatinib. Novartis therefore continues to recommend that the appropriate action for NICE is to issue a recommendation reminder instead of issuing new guidance that has the same conclusion as that reached in TA86.</td><td>400 mg/day imatinib. The Committee acknowledged that the consultees and commentators for this appraisal were given several opportunities to comment on the scope during the review proposal and appraisal processes. See FAD section 4.3.3.</td></tr>
<tr><td>Novartis Pharmaceuticals</td><td>3. Comments
<table>
<tr><th>Section in ACD</th><th>ACD text</th><th>Novartis Comment</th></tr>
<tr><td>1</td><td>n/a</td><td>If NICE goes ahead with Guidance, this section should include a recommendation allowing patients already receiving imatinib doses higher than 400 mg/day to continue with treatment until they and their clinicians consider it appropriate to change this treatment. Novartis believes that it is unfair to expect patients who have already been dose escalated and benefiting from the treatment to suddenly alter treatment when the guidance is issued. This is also in line with commentary in other NICE appraisals.</td></tr>
</table></td><td>Comment noted. As per FAD section 1.2. people who are currently receiving 600 or 800 mg/day imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours should have the option to continue therapy until they and their clinicians consider it appropriate to stop.</td></tr>
<tr><td>Novartis Pharmaceuticals</td><td>4.1.3 | EORTC trial ACD indicates that n = 473 | This is misleading as the total number of patients in the EORTC study was 946. It should be clarified that 473 was the total number of patients in the 400mg dose imatinib arm.</td><td>Comment noted. FAD amended accordingly.</td></tr>
<tr><td>Novartis Pharmaceuticals</td><td>4.1.3 | S0033 trial ACD indicates that n= 345 | This is misleading as the total number of patients in the S0033 study was 746.<br>It should be clarified that 345 pertained to the total number of patients in the 400mg dose imatinib arm.</td><td>Comment noted. FAD amended accordingly.</td></tr>
<tr><td>Novartis Pharmaceuticals</td><td>4.1.3 | ‘interim response data were reported for 68 people’ | Please specify the source of the interim data i.e. Rankin et al 2004 abstract because the S0033 trial data has been reported in several publications so referencing the source aids clarity</td><td>Comment noted. FAD amended accordingly.</td></tr>
<tr><td>Novartis Pharmaceuticals</td><td>4.1.3 | B2222 trial The ACD indicates that n = 73 | This is misleading as the total number of patients in the study was 147. It should be clarified that 73 was the total number of patients in the 400mg dose imatinib arm.</td><td>Comment noted. FAD amended accordingly.</td></tr>
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| **Novartis Pharmaceuticals** | 4.1.6 | 'The manufacturer of imatinib reported data from a confidential trial in their submission, which gave response to treatment in people who received increased doses of imatinib.' | This statement is incorrect; the confidential information/data in our submission was based on the results of a meta-analysis of the EORTC and SWOG trials and was not a separate trial different from these two main studies. Therefore the sentence should read: **"The manufacturer reported confidential data from a meta-analysis of the S0033 and EORTC studies."** | Comment noted. FAD amended accordingly. |
| **Novartis Pharmaceuticals** | 4.1.7 | "The retrospective cohort study reported that 4 of the 12 people (33.3%) who received an increased dose of imatinib (800 mg/day) after disease progression achieved either a partial response or had stable disease after treatment." | The Park et al publication actually states the following:<br>"The dose was increased to 600 mg/day in 12 patients (50%) and to 800 mg/day in the other 12 patients (50%). Following imatinib dose escalation to 800 mg, two patients (8.3%; 95% CI 0–20.3) achieved partial responses, and seven (29.2%) had stable disease." Therefore, in total, **nine patients** achieved either partial response/stable disease, not four. | Comment noted. The assessment report indicates that 5/12 patients that were given an escalated dose of 600mg/day imatinib showed either partial response or stable disease, whereas 4/12 patients given an escalated dose of 800 mg/day imatinib showed either partial response or had stable disease. The FAD remains unchanged as this section only describes patients receiving 800 mg/day imatinib (i.e. n=4), not all patients. |
| **Novartis Pharmaceuticals** | 4.1.13 | "Using interim data from this trial for 68 people, investigators estimated a median PFS after crossover of 4 months." | Please specify the source of the interim data i.e. Zalcberg 2004 abstract because the EORTC trial data has been reported in several publications so referencing the source aids clarity. | Comment noted. This comment refers to interim data from the S0033 trial. The FAD has been amended to highlight that the interim data is from a study by Rankin et al. |
| **Novartis** | 4.1.20 | "Interim data from | The full EORTC publication (Zalcberg 2005) | Comment noted. The Assessment Group described the 133 |

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| **Pharmaceuticals** | | this study also showed that 31% of people (absolute number not given) required the dose to be reduced from 800 mg/ day imatinib." | states that 70% of people did not require dose reduction, implying that **30%** required dose reduction, not 31%. | patients who crossed over to high-dose imatinib according to the study protocol. It is stated on page 1753 in the assessment report that: "...in those patients crossing over to high-dose imatinib but not according to study protocol, 70% did not require a dose reduction. The remaining analyses in this report are based on the 133 patients who crossed over to high-dose imatinib according to the protocol recommendations".'<br>Therefore, the FAD remains unchanged. |
| **Novartis Pharmaceuticals** | 4.3.2 | "The clinical specialists explained to the Committee that clinicians often consider increasing the dose of imatinib before offering treatment with sunitinib because imatinib is considered to have a more favourable adverse event profile, even at higher doses, than sunitinib." | Novartis considers it relevant to also include the following after the sentence in the ACD quoted on the left column: 'The UK National GIST guidelines also recommend dose escalating prior to switching therapy."<br>This should also be updated in the table on page 30 of ACD accordingly. | Comment noted. The Committee considered the UK guidelines for the management of GIST that were published in May 2009 during the second Committee meeting. The FAD has been updated to reflect the Committee's discussion on these guidelines. See FAD section 4.3.5. |
| **Novartis Pharmaceuticals** | 4.3.5 | "The committee heard that the **three studies** in which the dose of imatinib was increased from 400 mg to 800 mg/ day showed that approximately | There were only two studies in which the dose of imatinib was increased from 400 mg to 800 mg (EORTC study and S0033 study).<br>Therefore the statement should be changed to two studies, not three.<br>This should also be updated in table on page 30 of ACD accordingly. | Comment noted. In response to the manufacturer's comments on the ACD, the Assessment Group confirmed that the Park et al study also reported that 12 patients received an escalated dose of 800 mg/day imatinib following 400 mg/day imatinib, therefore 3 studies were considered available for assessment, not two. The FAD remains unchanged. |

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| | | one third of people had either a partial response or had stable response." | | |
| **Novartis Pharmaceuticals** | 4.3.8 | "The committee was aware that people in this study were treated with sunitinib after higher (600 or 800 mg/ day) rather than the lower (400 mg/ day) doses of imatinib..." | NICE TA179 states that 80% of patients receiving sunitinib had failed on higher doses of imatinib (higher than 400 mg but TA179 does not specify the exact imatinib dose on which they failed). Novartis believes this figure should be included to clarify the likely treatment algorithm.<br>This should also be updated in table on page 30 of ACD accordingly. | Comment noted. The Committee considered the data reported by the Assessment Group for the comparator treatment, sunitinib. The Committee noted that this evidence was mainly from an 'expanded access programme', in which regulators allow investigational drugs to be used to treat people with serious or immediately life-threatening diseases who cannot participate in clinical trials and who have no alternative therapy. The Committee was aware that people in this study were treated with sunitinib after receiving higher (600 or 800 mg/day) rather than lower (400 mg/day) doses of imatinib and did not necessarily reflect the population of interest in this appraisal – that is, people whose disease progresses on 400 mg/day imatinib (see FAD 4.3.9). |
| **Department of Health** | Thank you for the opportunity to comment on the appraisal consultation document and evaluation report for the above health technology appraisal.<br>I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation. | | | Comment noted. No action required. |
| **Royal College of Physicians** on behalf of **Sarcoma UK, Association of Cancer Physicians, GIST Support UK, The Institute of Cancer Research, Macmillan Cancer Support, NCRI, Sarcoma** | **ACD - Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours (part review of TA86)**<br><br>This response is submitted by an RCP registrar on behalf of the following organisations:<br><br><u>Patient organisations</u><br>Sarcoma UK<br>GIST Support UK<br>Macmillan Cancer Support Group<br>Rarer Cancers Foundation<br><br><u>Professional/medical organisations</u><br>Association of Cancer Physicians<br>The Institute of Cancer Research<br>NCRI Sarcoma Clinical Studies<br>Royal College of Physicians | | | Comment noted. No action required. |

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| **Clinical Studies Group, Rarer Cancers Foundation, Beating Bowel Cancer, Royal College of Radiologists, Bowel Cancer UK, Joint Collegiate Council for Oncology** | Beating Bowel Cancer<br>Bowel Cancer UK<br>Royal College of Radiologists<br>Joint Collegiate Council for Oncology<br><br>We are grateful for the opportunity to respond and would like to make the following comments to the questions posed. | |
| **Royal College of Physicians** | **1. Has all of the relevant evidence been taken into account?**<br><br>No. We do not believe that all of the relevant evidence has been taken into account due to the restrictive interpretation of the scope of this appraisal. We find this perverse. | Comment noted. The Committee noted that consultees had requested the review based on the belief that a large body of clinical evidence about imatinib had been published since 2004. The Committee noted that this appraisal is a part review of 'Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours' (NICE technology appraisal guidance 86), and the scope was to review recommendation 1.4 only, about whether the dose of imatinib should be increased following disease progression on 400 mg/day imatinib. During the Committee meeting, the Committee heard from the manufacturer that no new evidence on the effectiveness of increased doses of imatinib after disease progression on 400 mg/day imatinib has emerged since NICE technology appraisal guidance 86 was published in 2004. See FAD section 4.3.3. |
| **Royal College of Physicians** | When imatinib was first considered by NICE for the treatment of gastrointestinal stromal tumours (GIST) in 2004, evidence for a dose response relationship for imatinib in terms of progression-free survival was not considered admissible, because it had only been published in abstract form. A large randomised clinical trial that addressed this issue was published in the Lancet later the same year. In the 2004 Technology Appraisal (TA86) it is specifically stated that a full review of imatinib in GIST would take place in October 2007.<br>Since 2004, a large body of evidence has been published that has not been considered by the Review Assessment Group. For example, it is known that a significant subgroup of patients with a mutation in exon 9 of the KIT gene benefit | Comment noted. The Committee noted that consultees had requested the review based on the belief that a large body of clinical evidence about imatinib had been published since 2004. The Committee noted that this appraisal is a part review of 'Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours' (NICE technology appraisal guidance 86), and the scope was to review recommendation 1.4 only, about whether the dose of imatinib should be increased following disease progression on 400 mg/day imatinib. During the Committee meeting, the Committee heard from the |

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| | from the use of a larger dose of imatinib because the conformation of this altered protein is relatively unfavourable for imatinib binding. This observation was confirmed in a meta-analysis of European and North American trials involving 1640 patients. It is true that the meta-analysis did not show a statistically significant survival benefit, but this may be in part due to the small numbers and also to the efficacy of salvage therapy on progression. We are deeply concerned that this evidence was not considered by the Assessment Group. | manufacturer that no new evidence on the effectiveness of increased doses of imatinib after disease progression on 400 mg/day imatinib has emerged since NICE technology appraisal guidance 86 was published in 2004. See FAD section 4.3.3.<br><br>The Committee heard that data from the Gastrointestinal Stromal Tumor Meta-Analysis Group (metaGIST) was published in March 2010. However, these data were not included in the Assessment Group's economic analyses because the population was randomised to higher doses of imatinib at baseline and had not received treatment with 400 mg/day imatinib first. Therefore, the population in the metaGIST study was different from the population for this appraisal (see FAD 4.3.4) In addition, the Committee noted that data from metaGIST, in which people with exon 9 mutations started treatment on 800 mg/day imatinib, showed that there was no statistically significant difference in overall survival between people with exon 9 mutations treated with 400 mg/day imatinib compared with 800 mg/day imatinib (see FAD 4.3.8). |
| **Royal College of Physicians** | In conducting this appraisal a very narrow terms of reference has been used ie 'what is the evidence for clinical benefit from increasing the imatinib dose for patients with GIST progressing on imatinib 400 mg?' Since most of the data available concerning imatinib in GIST are derived from studies that investigated a starting dose of either 400mg or 800mg this means that the Assessment Group has discounted all that has been learnt concerning the molecular biology and pharmacokinetics of imatinib since 2004.<br>The result of the above is that the promised full re-appraisal of this technology has not, in our view, been performed. | Comment noted. This appraisal is a part review of 'Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours' (NICE technology appraisal guidance 86), and the scope was to review only recommendation 1.4 only of Technology Appraisal guidance 86, about whether the dose of imatinib should be increased to 600 mg or 800 mg/day following disease progression on 400 mg/day imatinib. Consultees and commentators for this appraisal were given the opportunity to comment on the appropriateness of this review during the scoping process See FAD section 4.3.3. |
| **Royal College of Physicians** | **2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**<br><br>No.<br>We believe that the clinical pathway which is followed by patients with advanced GIST (as part of standard clinical practice all over the world) has not been adequately considered. | Comment noted. The Committee discussed current clinical practice for the treatment of people with unresectable and/or metastatic GISTs following advice from clinical specialists and patient experts. The clinical specialists explained to the Committee that clinicians often consider increasing the dose of imatinib before offering treatment with sunitinib because imatinib is considered to have a more favourable adverse events profile, even at higher doses, than sunitinib. They also noted that if a |

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| | | person's disease fails to respond to higher doses of imatinib, it is common practice (in approximately 50% of people) to continue treatment with 400 mg/day imatinib in addition to best supportive care if the person tolerates imatinib. See FAD section 4.3.2. |
| **Royal College of Physicians** | We believe that substantial effort has been wasted assessing a 600mg/d dose which is rarely used in practice, and then most often as a temporary measure to control side-effects from the higher 800mg/d dose. | Comment noted. The 600 mg/day imatinib dose after disease progression on 400 mg/day imatinib is part of the scope of the review and therefore was considered by the Committee. |
| **Royal College of Physicians** | The critical clinical objective for patients with advanced GIST is to be able to maintain first-line treatment on imatinib for as long as possible. Relapse indicates resistance to the drug, a situation which is not reversible. Second-line and subsequent therapies are less effective than imatinib is in first-line. It is known that some patients remain responsive to imatinib for long periods (many years) while those who develop resistance, most often typified by secondary genetic mutations and new tumour growth, do not. | Comment noted. The Committee was aware that NICE technology appraisal guidance 179 recommends that patients have the option to receive treatment with sunitinib after disease progression on 400 mg/day imatinib. However, the clinical specialists explained to the Committee that clinicians often consider increasing the dose of imatinib before offering treatment with sunitinib because imatinib is considered to have a more favourable adverse event profile, even at higher doses, than sunitinib. Despite the lack of clinical trial evidence to demonstrate the effectiveness of increased doses of imatinib treatment, the Committee acknowledged that there is a perception among both patient experts and clinical specialists that treatment with 800 mg/day imatinib after disease progression on 400 mg/day imatinib may offer some benefit. See FAD section 4.3.2. |
| **Royal College of Physicians** | In this appraisal the escalated dose issues have been reviewed in isolation, with no consideration of individual patient opportunities to benefit from provision of an escalated dose of imatinib. There is evidence from clinical experience of the benefit attained by specific sub-groups of patients defined by genetic mutation analysis, most notably those patients with a primary showing the exon 9 mutation in KIT. | Comment noted. The Committee discussed whether benefits from increased doses of imatinib might be greater in certain subgroups of people. The Committee heard from the clinical specialists that there is some evidence suggesting that GISTs with certain mutations in the KIT gene are likely to be more or less sensitive to imatinib treatment. The clinical specialists suggested that the presence of an exon 9 mutation may be associated with a better outcome in people whose dose is increased to 800 mg/day imatinib. In addition, the clinical specialists explained that, although outside the current marketing authorisation, clinicians might choose to begin treatment with imatinib at 800 mg/day without having tried lower doses in people with confirmed exon 9 mutations. However, they explained that the clinical evidence supporting this practice is based on the experience of a small number of people. In light of |

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| | | the limited data available, the Committee noted that economic modelling for this subgroup would not be considered more robust than for the entire population. Therefore, the Committee concluded that there was not sufficient evidence to justify a separate recommendation for the use of 600 or 800 mg/day imatinib for people with exon 9 mutations whose disease had progressed on imatinib 400 mg/day. See FAD section 4.3.8. |
| **Royal College of Physicians** | Unfortunately, the manufacturer has not sought a product licence for the initial treatment of any particular group of patients with the 800mg/d dose of imatinib. We believe this is largely because, in the light of the almost universal acceptance that 800 mg is the appropriate dose for KIT exon 9 mutant GIST and the value of dose escalation on progression at the 400 mg dose, it did not appear to be commercially necessary to do so. | Comment noted. |
| **Royal College of Physicians** | We believe there to be some significant inaccuracies in the ACD and its Summary.<br><br>First paragraph 4.3.3:- 'no randomized controlled trials were identified on the effectiveness of an increased dose of imatinib compared with sunitinib or best supportive care'. In fact evidence was submitted verbally that a clinical trial comparing sunitinib with imatinib at 800mg in patients progressing on 400mg had been initiated by Pfizer (Study A6181112). Unfortunately, this study failed to accrue sufficient patients, except in the UK and South Korea, the only countries where sunitinib had not yet been approved for reimbursement. It was closed shortly after sunitinib was approved for the second line treatment of GIST by NICE. | Comment noted. Section 4.3.3 describes the results of the literature search conducted by the Assessment Group (that is, no randomised controlled trials were identified on the effectiveness of an increased dose of imatinib compared with sunitinib or best supportive care). While the Committee heard from the clinical specialists that a trial comparing high-dose imatinib with sunitinib had been stopped after it failed to recruit a sufficient number of people, this trial was not published and therefore was not identified by the Assessment Group. The Committee also heard from the manufacturer that there are no ongoing trials that address the decision problem in this appraisal. The Committee concluded that the Assessment Group had made a good effort to include all available data relevant to this appraisal in its report but was concerned about the paucity and nature of the evidence available. See FAD section 4.3.4. |
| **Royal College of Physicians** | Para 4.3.9 reports that clinical specialists stated that the original criteria in TA86 remain valid, specifically:- 'continuing imatinib is recommended only if a response to initial treatment is achieved within 12 weeks'. Our experts, who attended the Committee, do not recall this being discussed as such and do not endorse the statement. Patients with exon 9 mutant GIST would appropriately receive the larger dose. In addition, it was correctly assumed by the Assessment Group (page 91 of the Evaluation Report), that imatinib can be part of best supportive care in progressing patients. This is because of the heterogeneity of the disease, | Comment noted. The stopping rule was discussed at the appraisal committee meeting. The Committee heard that recommendations in NICE technology appraisal guidance 86 for stopping imatinib 400 mg/day were not supported by clinical specialists. See FAD section 4.3.14. |

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| | even if partially resistant, and the ability of the drug to contribute greatly to symptom control in some patients. | |
| **Royal College of Physicians** | We believe that the development of advances in imatinib blood level testing, which allow imatinib levels in the blood to be assessed, has been ignored. Ironically it is often patients whose liver function improves on treatment with imatinib whose blood levels fall. Although this is not standard clinical practice, because imatinib blood level testing facilities are not yet widespread, specialists treating GIST worldwide now recognise the importance to individual outcomes of identifying when patients' levels of active drug are falling and correcting that situation with an escalated dose. An arrangement for imatinib blood level testing for patients with GIST is now in place, funded by Novartis, as it is for patients with CML, in a laboratory at King's College Hospital, London. This is available to patients from anywhere in the UK. It is clear that low trough levels correlate with poor response and shorter response duration, hence the justification for increasing the dose. This is also being studied prospectively in the UK, at the Christie Hospital, and at the Dana Farber Cancer Center in the US. | Comment noted. The Committee heard from the patient experts that measuring plasma concentrations of imatinib could be a major advantage, because it might allow an individualised approach to the dosing of imatinib. However, the clinical specialists noted that this does not happen in routine UK clinical practice, and the Committee noted that no data had been presented to demonstrate an association between plasma concentrations and outcomes. The Committee concluded that while measuring plasma concentrations of imatinib might potentially be of benefit, it could not base any recommendations on this because of the lack of evidence and because it was not used in routine clinical practice. See FAD section 4.3.7. |
| **Royal College of Physicians** | It is true that dose escalation would not be valuable in the case of imatinib resistance due to a secondary mutation, but in about a third of cases resistance is due to other causes, including less favourable primary mutations, or the lack of a known driving mutation, but also amplification of the KIT gene and upregulation of drug transporter mechanisms in tumour tissue. This is the same percentage of patients that were shown to benefit from crossing over from 400 mg to 800 mg imatinib on progression in both the 62005 European-Australasian study and the S0033 North American study. | Comment noted. The Committee discussed whether benefits from increased doses of imatinib might be greater in certain subgroups of people. The Committee heard from the clinical specialists that there is some evidence suggesting that GISTs with certain mutations in the KIT gene are likely to be more or less sensitive to imatinib treatment. The clinical specialists suggested that the presence of an exon 9 mutation may be associated with a better outcome in people whose dose is increased to 800 mg/day imatinib. The Committee also understood that mutational analysis in people with progressive disease had a limited role, if any, in clinical decision-making about increasing imatinib doses. Therefore, the Committee concluded that there was not sufficient evidence to justify a separate recommendation for the use of 600 or 800 mg/day imatinib for people with exon 9 mutations whose disease had progressed on imatinib 400 mg/day. |
| **Royal College of Physicians** | The relative paucity of evidence is directly attributable to the rarity of this disease. However, the failure to allow clinicians to act on their knowledge serves only to condemn groups of patients to resistant and fatal disease. These patients can be individually prognostically identified and can experience high quality of extended | Comment noted. The Committee heard that consultees noted that the paucity of clinical evidence related to this appraisal was directly attributable to the rarity of GIST. However, the Committee acknowledged that, while the rarity of the disease did contribute to the paucity of evidence, more could have been |

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| | life with, in some cases, no evidence of active disease for some years. | done to describe the clinical experience that exists. The consultees and commentators echoed the Committee's concerns that a disease register had not been established since the publication of NICE technology appraisal guidance 86. See FAD section 4.3.15. |
| **Royal College of Physicians** | In particular, we would like to identify the conflicting nature of the discussion on 'end-of-life' in paragraphs 4.3.16 and 4.3.17. While not meeting the strict criteria set for an 'end-of-life' treatment a failure to prescribe escalated dose imatinib to a suitable patient will accelerate that patient's pathway to end-of-life. This conflict is not resolved by the discussion in the ACD, which we believe does not address the intent of Ministers when the 'end-of-life' review was proposed in 2008. | Comment noted.<br>The consultee may be referring to the 'End-of-life-care' programme http://www.endoflifecareforadults.nhs.uk/ launched in 2008. This programme is not related to the End-of-life medicines supplementary advice given to the Appraisal Committees in January 2009.<br>The Committee took into account the end-of-life criteria from this supplementary advice, but agreed that the evidence for this life extension could not be considered sufficiently robust, considering the uncertainty about the assumptions in the economic model, and the lack of data comparing clinical effectiveness. The Committee therefore concluded that increased doses of imatinib following disease progression at 400 mg/day imatinib did not meet the criteria for being a life-extending, end-of-life treatment. See FAD section 4.3.19. |

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| **Royal College of Physicians** | However, the most negative reflection on this particular technology appraisal process is to be found in the evaluation report (on which we have commented separately). Sunitinib was approved by NICE for the second line treatment of imatinib-refractory GIST on the basis of a patient access scheme agreed with the company. The technology appraisal TA179G, published in September 2009 indicates that the best estimate for the incremental cost-effectiveness ratio (ICER) for sunitinib after disease progression on imatinib was £31,800 per quality adjusted life year gained. This was based on the evidence presented to NICE by the Review Group report prepared by the Peninsula Technology Assessment Group. However, on this occasion the Assessment Group report, prepared by the Aberdeen Technology Assessment Group concludes on the basis of their modeling, that a treatment pathway that takes patients who progress on imatinib 400 mg immediately to sunitinib, pathway 7 in Fig 5, produces an incremental cost per QUALY of £272,365 (Table 16).<br>If the modeling is so inaccurate as to produce an estimate >8 fold higher than the one published in TA179, we wonder how a rational decision can be made not to recommend the use of imatinib 800 daily on progression on the grounds of a lack of cost-effectiveness. We believe this threatens the credibility and consistency of the process and needs addressing. As all of the data on sunitinib were presumably available to the Aberdeen group how were they able to produce such an incredible, in the true sense of the word, result? | Comment noted. As per the Assessment Group's response to comments on the ACD, the majority of the population (>80%) in the randomised controlled trial considered in TAR179 had predominantly progressed on previous doses of imatinib >400 mg/day. As this appraisal was concerned with those progressing on the 400 mg/day dose, the study populations are different. Very sparse data were available for those progressing on 400 mg/day imatinib, and so it is repeatedly stated in the assessment report that the results are surrounded by considerable imprecision and are potentially unreliable (see pages 69, 70, 81, 89, and 90 of the assessment report). Sensitivity analyses reported for TA179 provide estimated ICERs in excess of the £272,365 figure in the assessment report (see page 90 of TAR179). This illustrates the considerable uncertainty that surrounds the estimates of cost-effectiveness, which in the case of TA179 were caused by differing methods of estimating hazard ratios, and assumptions about whether the NHS would incur the first cycle costs of sunitinib. |
| **Royal College of Physicians** | **3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**<br>No.<br><br>We note that no other country in Europe (nor the USA) denies 800mg/d of imatinib to patients, either as first-line or second-line treatment. The numbers of patients affected is very small. Exon 9 mutation is seen in about 11% of patients with primary GIST – maybe 35-40 new patients a year in England and Wales in the advanced/metastatic setting. While one accepts that resources are not limitless and the NHS is right to have a focus on cost-effectiveness, the clinical effectiveness of imatinib in the treatment of GIST cannot be denied. It is the view of our organisations that the total cost of giving clinicians discretion in prescribing imatinib will have little overall financial impact on the NHS. | Comment noted. The Committee appreciated the point made by consultees and commentators that, as this appraisal affected only a small group of people, giving clinicians the discretion to prescribe imatinib at doses higher than 400 mg/day would have little overall financial impact on the NHS. However, the Committee emphasised that (in line with NICE's 'Guide to the methods of technology appraisal') the potential budget impact of the adoption of a new technology does not determine its decision. See FAD 4.3.14. |
| **Royal College of Physicians** | The discussion on appropriate utility scores from the EQ5D in paragraphs 4.3.13 and 4.3.14 are very unsatisfactory.<br>An asymptomatic GIST patient may have an EQ5D score of 1 at diagnosis and the | Comment noted. The Committee heard from patient experts that the health measures defined in the NICE reference case, such as the EQ-5D, might not capture the benefits that people gain |

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| | same after five years of first-line imatinib. The cost-per-QALY would be infinite. However, without treatment this patient would have died. Similarly it is possible for a radically disabled patient to have a very low, even a minus, score at diagnosis, which is not affected by treatment, although the treatment keeps them alive. Again the cost-per-QALY may be infinite. Between these two extremes every kind of EQ5D score is possible. | from imatinib treatment. The Committee considered the utility value used in the Assessment Group's economic model for imatinib and sunitinib (0.935). The Committee considered that this value was implausibly high and noted that this value had been derived from three out of nine clinicians who had responded to a questionnaire. Although the Assessment Group carried out some sensitivity analyses that varied the utility value, the Committee was not convinced that the most plausible value had been used and considered that this added further uncertainty to the model. The Committee also considered that using a more appropriate utility value would probably increase the ICER because the difference between the utility value of the active treatment and comparator would be smaller. Therefore, the Committee concluded that collecting utility data is important for any future informed decision-making for this population. See FAD section 4.3.13. |
| **Royal College of Physicians** | Choosing a 'generic' point on which to base calculations is, we believe, a deeply flawed concept given the extreme range feasible among GIST patients. Without reliable data, and without open and transparent criteria for making a judgement on an appropriate range of scores, reviewing that range in the light of the distribution of utility scores from a real patient group, the process is open to bias and ill-informed conjecture. This is evident in para 4.3.14 where the Committee, without reference to clinical expertise and ignoring the views of expert witnesses, makes assumptions without any evidence base. We do not believe that this conjecture can be described as a 'sound and suitable base' for guidance recommendations to the NHS. | Comment noted. Please see comment immediately above. |
| **Royal College of Physicians** | We also observe that there is a striking dissonance between the recommendations made in this ACD and the recent announcement from Cancer Research UK of active steps towards treating cancer patients on an individual genetically identified basis, rather than a histologically defined disease basis. GIST is one of a growing number of cancers for which genetic characterisation can not only provide valuable prognostic information but can also be used as a guide to the most effective therapy. We believe that this has been ignored within the appraisal. | Comment noted. The Committee understood from the clinical experts that mutational analysis in people with progressive disease had a limited role, if any, for clinical decision making about increasing imatinib doses. See FAD 4.3.8. |
| **Royal College of Physicians** | Another aspect of GIST management with imatinib that should have been considered in a comprehensive review of the technology is the issue of CD117 negative GIST. In TA86, it is recommended that treatment with imatinib be | Comment noted. The scope of the review clearly defines that the population would only include people with KIT (CD117) positive |

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| | confined to tumours expressing the antigen CD117, i.e. KIT. However, we now know that GIST can be driven by mutations in the PDGFRA gene, and in some of these tumours CD117 is not expressed. In a minority of other cases CD117 expression is low, but a characteristic mutation in KIT is found, confirming the diagnosis. Additionally, another antibody, DOG1, can be used to make a diagnosis of GIST if CD117 is equivocal, as discussed by Dr Robin Reid at the appraisal meeting. | unresectable and/or metastatic GIST. |
| **Royal College of Physicians** | The Committee recommends, in the ACD, that further research be conducted on the use of mutational analysis to predict individual responses to treatment. However, the outcome of the ACD makes this futile with respect to imatinib. It will not be possible to collect additional data on the relationship between imatinib 800mg and survival in patients with KIT exon 9 mutant disease if this dose is not available. Similarly, the problem with implementing a national register and plasma level measurements has been a lack of funding.<br>We believe that the recommendations in this ACD, if carried forward, will deny physicians and their patients the opportunity to apply their knowledge of the driving mutations in this disease and will thus deny appropriate treatment to a rare cancer group. | Comment noted. NICE can only issue guidance in accordance with the marketing authorisation. During the appraisal committee meeting the Committee heard from the manufacturer that a national register for people with GISTs is currently being set up, with pilot testing expected to begin by the end of 2010. |
| **Royal College of Physicians** | **4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?**<br>Discrimination on grounds of rarity of disease is not unlawful. However, we believe it to be unethical and possibly immoral by the common standards of society. There may also be a case for it being illegal if through unreasonability or irrationality a patient or group of patients is unfairly discriminated against.<br>We believe that the argument – 'the absence of evidence is not evidence of absence' - applies to the disease setting being examined here. The fact is that the scarcity of patients with GIST, and the even scarcer incidence of those with the less common mutations evident in the disease, makes prospective studies (even on an international scale) difficult. For NICE to make judgements on issues for which there are no studies (eg 600mg/d of imatinib) or for it to seek answers to specific questions which are not of interest outside the UK (and thus of no value to non-UK investigators), is therefore discriminatory. | Comment noted. The Committee considered whether its recommendation was associated with any potential issues related to equality. The Committee noted comments made during consultation on the appraisal consultation document that not recommending 600 or 800mg/day of imatinib after disease progression with 400mg/day imatinib discriminates against people with rare diseases. The Committee also noted the respective consultees' comments that having a rare disease does not itself constitute one of the protected characteristics in the current equalities legislation or the Equality Act. However, the Committee was aware that under the Human Rights Act groups of people other than those addressed under the equalities legislation must also be considered. The Committee therefore explored if its recommendation unfairly disadvantaged any groups within the remit of this appraisal. The Committee had addressed whether the technology met end-of-life criteria and noted that while it met the criteria for a rare disease, the estimate related to the extension of life remained uncertain. The Committee took into account the lack of robust clinical evidence |

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| | | for a survival benefit of higher doses of imatinib, specifically for the subgroup of people that have been reported to respond better, that is, people with an exon 9 mutation. The Committee was aware of section 6.2.14 of the NICE methods guide that states: "The potential budget impact of the adoption of a new technology does not determine the Appraisal Committee's decision." The Committee was also aware that the paucity of clinical evidence was not related only to the rarity of indication, and recognised that a previous appraisal had called for the manufacturer to establish a disease registry including data related to treatment which had not been done. Lastly, the Committee was aware that options for effective treatment for this group of patients exists in that NICE technology appraisal guidance 179 recommends that patients have the option to receive treatment with sunitinib after disease progression on 400 mg/day imatinib.<br><br>Given the uncertainty about whether higher doses of imatinib provide a survival benefit for people with unresectable and/or metastatic GIST, and the availability of options of alternative treatment having had disease progression, the Committee was satisfied that its recommendation was consistent with NICE's obligations under the equalities legislation and the requirement for fairness. See FAD section 4.3.19. |
| **Royal College of Physicians** | However, evidence is available to be assessed, even if it is in study sub-groups, small case series, unpublished studies and, in the case of patient experience, anecdotal. In failing to pay regard to this evidence, and making judgements without taking account of this data, the recommendations could be argued to be discriminatory. | Comment noted. During the Committee meeting, the Committee heard from the manufacturer that no new evidence on the effectiveness of increased doses of imatinib after disease progression on 400 mg/day imatinib had emerged since NICE technology appraisal guidance 86 was published in 2004. See FAD section 4.3.3. The Committee made every possible effort to look at evidence for the increased doses of imatinib, even considering interim data from the trials.<br><br>However, since the previous appraisal of imatinib (NICE technology appraisal guidance 86), there is no new good-quality data on the clinical and cost effectiveness of increasing the dose of imatinib after disease progression on 400 mg/day. The Committee took all available evidence into account, along with comments from the patient experts, clinical specialists, |

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| | | Assessment Group, manufacturer, and those who commented on the assessment report. It concluded that the current available evidence does not justify a positive recommendation for the use of imatinib at increased doses of 600 mg/day and 800 mg/day as an appropriate use of NHS resources for the treatment of people with unresectable and/or metastatic GISTs whose disease has progressed on treatment with 400 mg/day imatinib. See FAD section 4.3.20. |
| **Royal College of Physicians** | In this particular case, some of the patients who would be denied effective first-line treatment can be identified through mutation analysis. The position of receiving this prognostic information and then selectively being denied access to appropriate treatment, can also be argued as discrimination against a very rare patient sub-group. | Comment noted. The Committee considered whether its recommendation was associated with any potential issues related to equality. The Committee noted comments made during consultation on the appraisal consultation document that not recommending 600 or 800mg/day of imatinib after disease progression with 400mg/day imatinib discriminates against people with rare diseases. The Committee also noted the respective consultees' comments that having a rare disease does not itself constitute one of the protected characteristics in the current equalities legislation or the Equality Act. However, the Committee was aware that under the Human Rights Act groups of people other than those addressed under the equalities legislation must also be considered. The Committee therefore explored if its recommendation unfairly disadvantaged any groups within the remit of this appraisal. The Committee had addressed whether the technology met end-of-life criteria and noted that while it met the criteria for a rare disease, the estimate related to the extension of life remained uncertain. The Committee took into account the lack of robust clinical evidence for a survival benefit of higher doses of imatinib, specifically for the subgroup of people that have been reported to respond better, that is, people with an exon 9 mutation. The Committee was aware of section 6.2.14 of the NICE methods guide that states: "The potential budget impact of the adoption of a new technology does not determine the Appraisal Committee's decision." The Committee was also aware that the paucity of clinical evidence was not related only to the rarity of indication, and recognised that a previous appraisal had called for the manufacturer to establish a disease registry including data related to treatment which had not been done. Lastly, the |

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| | | Committee was aware that options for effective treatment for this group of patients exists in that NICE technology appraisal guidance 179 recommends that patients have the option to receive treatment with sunitinib after disease progression on 400 mg/day imatinib.<br>Given the uncertainty about whether higher doses of imatinib provide a survival benefit for people with unresectable and/or metastatic GIST, and the availability of options of alternative treatment having had disease progression, the Committee was satisfied that its recommendation was consistent with NICE's obligations under the equalities legislation and the requirement for fairness. See FAD section 4.3.19. |
| **Royal College of Physicians** | There is one other issue about this appraisal. Imatinib was first reviewed by NICE in 2003/4. Its decision included recommendations to the NHS that a national register of GIST patients and their treatment should be established. This has not occurred. It is clear that such a register might have met some of the needs of this technology review, and the call for such a register is renewed in the ACD.<br>That the NHS failed to implement that recommendation in 2004, and that the failure has contributed to this decision (albeit as yet a draft), is of very serious concern. | Comment noted. During the appraisal committee meeting the Committee heard from the manufacturer that a national register for people with GISTs is currently being set up, with pilot testing expected to begin by the end of 2010. See FAD section 4.3.11. |
| **Royal College of Physicians** | References provided:<br>1. 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.<br>2. Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients. J Clin Oncol 28: 1247-1253.<br>3. 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.<br>4. Blanke CD, Demetri GD, von Mehren M et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. J Clin Oncol 2008; 26: 620-625.<br>5. Zalcberg JR, Verweij J, Casali PG et al. Outcome of patients with | Comment noted. No action required. |

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| | 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. | |
| **Welsh Assembly Government** | Thank you for giving the Welsh Assembly Government the opportunity to comment. Please note that we have no comment to submit at this stage. | Comment noted. No action required. |
| **Royal College of Nursing** | **Introduction**<br>The Royal College of Nursing (RCN) was invited to review the Appraisal Consultation Document (ACD) for Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours (part review of TA86)<br>Nurses working in this area of health reviewed the consultation documents on behalf of the RCN.<br>**Appraisal Consultation Document – RCN Response**<br>The Royal College of Nursing welcomes the opportunity to review this document. The RCN's response to the four questions on which comments were requested is set out below:<br>i) **Has the relevant evidence has been taken into account?**<br>The evidence should include all relevant current evidence. | Comment noted. No action required. |
| **Royal College of Nursing** | ii) **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?**<br>We would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by patients with advanced GIST. The preliminary views on resource impact and implications should be in line with established standard clinical practice. | Comment noted. The Committee discussed current clinical practice for the treatment of people with unresectable and/or metastatic GISTs. Despite the lack of clinical trial evidence to demonstrate the effectiveness of increased doses of imatinib treatment, the Committee acknowledged that there is a perception among both patient experts and clinical specialists that treatment with 800 mg/day imatinib after disease progression on 400 mg/day imatinib may offer some benefit. See FAD section 4.3.2. |
| **Royal College of Nursing** | iii) **Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?**<br>Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee. We note that a small number of patients are affected by this condition, 900 per year in the UK. We note that without treatment GISTs progress and will eventually metastasise. It is, therefore, regrettable that the draft recommendations deny this group of patients access to this health technology for whom prognosis is stated to be poor with a generally survival rate of two years | Comment noted. The Committee was aware that NICE technology appraisal guidance 179 recommends that patients have the option to receive treatment with sunitinib after disease progression on 400 mg/day imatinib. See FAD section 4.3.2. |

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| | without further treatment. | |
| **Royal College of Nursing** | iv) **Are there any equality related issues that need special consideration that are not covered in the ACD?**<br>None that we are aware of at this stage. We would however, ask that any guidance issued should show that equality issues have been considered and that the guidance demonstrates an understanding of issues concerning patients' age, faith, race, gender, disability, cultural and sexuality where appropriate. | Comment noted. The Committee was satisfied that its recommendation was consistent with NICE's legislative obligations under the equalities legislation and the requirement for fairness. See FAD section 4.3.19. |
| **Royal College of Pathologists** | The Royal College of Pathologists have no comments to submit on the ACD document for the above appraisal. | Comment noted. No action required. |

**Comments received from commentators**

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| **NHS Quality Improvement Scotland** | To the best of my knowledge I believe all the relevant evidence on the subject has been taken into account.<br>The summaries of Clinical and Cost effectiveness are reasonable interpretations of the evidence, the provisional recommendations are sound and a suitable basis for guidance to the NHS.<br>I do not believe there are aspects of the recommendations that need particular consideration to avoid unlawful discrimination. | Comment noted. No action required. |
| **Pfizer** | Thank you for the opportunity to comment on the appraisal consultation document for Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours.<br>We have no substantive challenges with respect to the content of the document. Pfizer oncology recognises the complexities associated with assessing the cost-effectiveness of treatments for people with rarer cancers. Because of this we believe that there is a strong case for greater pragmatism in evaluating these medicines. | Comment noted. No action required. |