Comments from Novartis Pharmaceuticals UK Limited on the Appraisal Consultation Document (ACD) for the Health Technology Appraisal of Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours (part review of technology appraisal guidance 86)

Thank you for your invitation to comment on the above referenced Appraisal Consultation Document (ACD) and accompanying documents, which were released on the 22nd of June 2010.

Our response is provided in three sections:

1. Summary
2. Review process
3. Comments

1. Summary

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 400mg. 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.

2. Review process

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:

- 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.

- Defer the decision on if and how to update the published guidance to a future date.
- Incorporate the published guidance into a clinical guideline and withdraw the appraisal when the guideline is published.

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 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.

3. Comments

Section in ACD	ACD text	Novartis Comment
1	n/a	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.
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.
	ACD states that the interim response data were reported for 97 people	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
	S0033 trial ACD indicates that n = 345	This is misleading as the total number of patients in the S0033 study was 746. It should be clarified that 345 pertained to the total number of patients in the 400mg dose imatinib arm.
	'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
	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.
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."**

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: "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.
4.1.13	"Using interim data from this trial for 68 people, investigators estimated a median progression-free survival 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.
4.1.20	"Interim data from this study also showed that 31% of people (absolute number not given) required the dose to be reduced from 800 mg/ day imatinib."	The full EORTC publication (Zalcberg 2005) states that 70% of people did not require dose reduction, implying that **30%** required dose reduction, not 31%.
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." This should also be updated in the table on page 30 of ACD accordingly.
4.3.5	"The committee heard that the	There were only two studies in which the

	three studies in which the dose of imatinib was increased from 400 mg to 800 mg/ day showed that approximately one third of people had either a partial response or had stable response."	dose of imatinib was increased from 400 mg to 800 mg (EORTC study and S0033 study). Therefore the statement should be changed to two studies, not three. This should also be updated in table on page 30 of ACD accordingly.
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. This should also be updated in table on page 30 of ACD accordingly.