Comments from Novartis on the Assessment Report for the Health Technology Appraisal of imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours (part review of TA86)

Thank you for your invitation to comment on the above Assessment Report prepared by Aberdeen Health Technology Assessment Group. This submission is structured as follows:

1. Introduction
2. Summary of key points raised in the report
3. Detailed discussion of key issues
4. Other comments
5. Conclusion

1. Introduction

As presented in our submission of 23 November 2009, since the original publication of TA86 almost six years ago, clinical practice has evolved to include dose escalation to 600mg or 800mg imatinib for patients whose disease progresses on 400mg imatinib. Dose escalation is considered to be an effective treatment option which provides considerable benefits to patients whose disease has progressed. As a result, the option of imatinib dose escalation has been included in the UK National GIST Guidelines[1]. However, due to the limited amount of data available from the key clinical studies and the paucity of data comparing imatinib dose-escalation to sunitinib and best supportive care (BSC), we were unable to submit a sufficiently robust economic analysis which would meet the scope of this appraisal.

We note that the Assessment Group (AG) has conducted a comprehensive review of the evidence base on dose escalation for patients progressing on 400mg imatinib dose, and looked to model the clinical and cost effectiveness of imatinib dose escalation. However we have concerns about the quality of the data that has been used to inform the economic analysis and we believe that the results of this analysis are subject to uncertainty, bias and imprecision, and therefore are misleading for the decision maker and insufficient to support meaningful policy conclusions.

The evaluation of the assessment report below serves to underline our suggestion, as per our previous correspondence, that NICE reconsiders the part review of TA86 and issues a recommendation reminder instead of issuing new guidance.

2. Summary of the key points raised in the Assessment Report

We fully agree with the summary points below that were highlighted by the AG in the Assessment Report (AR), which are in line with the limitations discussed in our original submission.

2.1. Evidence limitations: comparative data

- *Studies published on the clinical effectiveness of best supportive care prior to the licensing of imatinib were not eligible for this review as our population of interest was those who had failed on imatinib at 400 mg/day, therefore all studies published prior to the availability of imatinib automatically failed to meet our inclusion criteria because best supportive care at that time could not possibly have been provided following failure of treatment with imatinib at a dose of 400 mg/day.* (page 20 of AR)
- *Much of the evidence base for sunitinib generally relates to its use following the failure of escalated doses of imatinib rather than failure on 400 mg/day, suggesting that the role of sunitinib is seen more as a third line treatment rather than a potential comparator to 600 or 800 mg/day imatinib treatment.* (page 90 of the AR)

2.2 Evidence limitations: imatinib data

- *The nature of the evidence base for patients who progress on 400 mg/day imatinib and receive escalated doses of 600 or 800 mg/day was observational and therefore open to extensive bias.* (page 84 of the AR)
- *The lack of quality data as well as lack of data itself severely limited both assessments of clinical and cost effectiveness*. (page 90 of the AR)

2.3 Economic evaluation limitations

- *The results of the economic analysis are based upon sparse data that are potentially biased and are surrounded by considerable imprecision.* (page 82 of the AR)

- *The economic model could not consider cost-effectiveness of treatment of patients with specific gene mutations due to lack of data.* (page 82 of the AR)
- *There was a lack of evidence on quality of life outcomes, which may be of fundamental importance to patients given the potentially palliative nature of treatment following progression, and there was also lack of evidence on best supportive care.* (page 90 of the AR)
- *A lack of data also prevented a comparative analysis of adverse events between the intervention and comparator treatments.* (page 90 of the AR)

3 Detailed discussion of key issues

In this section we will discuss the main issues with the data that were applied to the economic model, and how these data limitations severely curtail any meaningful conclusions.

3.1. The probability of death in the best supportive care (BSC) arm

We believe that the data used by the AG in the BSC arm was drawn from a different patient population compared to the population under review.

Firstly, the probability of death in the BSC arm was based on a pooled estimate from three retrospective reviews[2,3,4] of patients with gastrointestinal (GI) sarcomas or leiomyosarcomas (LMS) who were treated with surgery between 1951 and 1998. The three studies did not meet the inclusion criteria set out by the AG when they conducted the systematic review. It is important to note that these reviews were conducted before the awareness of GIST as a distinct tumour entity and there was no KIT (CD 117) testing conducted at the time. The molecular marker KIT (CD117) was introduced for diagnosing GIST in 2000 and was therefore not used in any previous studies (HTA monograph 2005[5]). The KIT (CD 117) receptor is an important and appropriate diagnostic marker for the diagnosis of GIST and the period during which these studies were conducted raises doubts about the proportion of patients in the studies who were in fact GIST patients. The Assessment Group concurs with this view, stating that *'studies that were published before the introduction of imatinib were not relevant to this review as the population of interest were patients failing 400mg imatinib.'* (AR page 20).

Thus the patient population from these studies used to estimate the probability of death, and hence survival for BSC patients, is different from the patient group that is of interest to this review. The current population of interest is that of patients with KIT (CD 117) positive unresectable and or KIT (CD 117) positive metastatic gastro-intestinal tumours who have failed 400mg imatinib treatment.

In addition, part of the inclusion criteria for the EORTC[6] and SWOG (S0033)[7] trials (main source of the imatinib survival and response estimates used in the model) stated that patients must have distantly metastatic or unresectable disease. A 10% five year survival rate for patients who had partial resection reported in figure 1 of the McGrath publication[3] and a 9% five year survival rate for patients who had partial resection reported in figure 1 of the Pierie publication[4] were pooled together to estimate survival for BSC. The patient population in the reviewed papers that were used to estimate the probability of death (survival) in the BSC arm were patients with resectable sarcomas who received either complete or partial resection. Therefore it does not seem clinically plausible to expect the same survival rate from patients with resectable sarcomas and those with unresectable metastatic GIST because it is unlikely that the clinical characteristics of these two patient populations will be similar.

Secondly, the typical BSC patient in this review should have failed imatinib 400mg, as evidenced by disease progression and then not dose escalated. The patient population in the studies used to estimate survival rate for the BSC arm had not received prior imatinib therapy as it was not available at the time. We therefore believe that the pooled BSC probability of death (survival) estimate derived from these studies is not representative of the survival of the BSC patients covered under this review. Not only are the data from an inappropriate population, they are non-randomised, non-comparative and therefore prone to bias. Indeed the AG acknowledged these limitations on pages 63 and 64 of the AR by stating that *'the data sources used would provide imprecise and potentially biased estimates of the probability of death for BSC.'*

We stress that the estimation of the BSC probability of death (and therefore survival) based on pooling of observational data that are non-comparative, non-randomised and possibly based on a different population to the population under review makes the estimated survival for the BSC arm potentially biased and unreliable for use in an economic analysis. The extent of bias these BSC estimates may produce is

highlighted by the AG where the mortality estimates used in the model suggest that sunitinib has a higher mortality than BSC.

In summary, there is a lack of data on the prognosis of patients who progress on 400mg imatinib but are not dose escalated. These are the patients whom, for the purposes of this review, will be in the BSC comparative arm of the economic analysis. In our submission we highlighted that the data on the BSC group xxx xxx xxxxxxxxx xxxxxxxas those patients whose disease progressed on 400mg imatinib dose, but did not dose escalate, wxxx xxx xxxxxxxx xx xxxxx xxxxxxx xxxxxxxxxxxere. For example, in the EORTC and SWOG studies, txx xxx xxxxxxxx xxx xxxxxxxxxx xx xxxxx xxx xxxx xxx xxxxxxxx xx xxx xxxxxxxx xxxx[8] could have provided a robust estimate of the survival probability in the BSC arm within the economic model. The patient population used by the AG to estimate BSC survival is neither appropriate for this review nor based on robust data sources and therefore the estimates are potentially biased and imprecise for use in an economic analysis.

3.2. Probability of death for 600mg and 800mg imatinib doses

The way in which the AG estimated the probability of death for 600mg imatinib is unclear. The probability of death for the 600mg imatinib dose was estimated to be 45% as reported in the AR. This estimate was derived from the B2222 study published by Blanke et al[9], although this estimate cannot be verified from the publication. We believe that this mortality rate was calculated by applying the 5 year survival rate from patients originally randomised to 400mg or 600mg imatinib dose to 11 patients who responded after being dose escalated from the 400mg arm following disease progression. We therefore consider that it is inaccurate to use this mortality rate to estimate the survival of patients who had partial response or stable disease after dose escalation from 400mg imatinib. In addition, the sample size is too small to be relied upon as a robust estimate of the survival rate of patients escalated to 600mg imatinib dose.

Given that the B2222 trial was not designed to assess dose escalation, we reiterate, as per our submission, that it is likely that the patients who were dose escalated might have exhibited certain clinical characteristics that differed from those who were not dose escalated after disease progression with 400mg imatinib treatment.

The same concern applies to the patients who were originally randomised to 400mg and 800mg imatinib in the S0033 trial. The use of data from the 800mg crossover group is likely to produce biased estimates of the probability of death in that patient group because the trial was not designed to assess dose escalation and thus patients were not randomised to dose escalate on disease progression. The uncertainty in the analysis becomes even more pronounced when you consider that the comparative data on the probability of death is derived from a pooled rate from three observational studies with populations that are different to the population of interest under this review, as highlighted earlier.

We consider that the incremental survival benefits resulting from comparing the 600mg and 800mg imatinib (based on small sample sizes identified from trials that were not intended to assess dose escalation) with the BSC arm (pooled from observational studies not relevant to this review) are highly biased and misleading. It is thus impossible to confidently conclude that the estimates of cost effectiveness reported in the AR, and based on these efficacy estimates, are robust and are fit to be used as a basis for decision making.

3.3. Response rates to 600mg and 800mg imatinib dose escalation

The response rates to 600mg and 800mg imatinib doses used by the AG were based on small patient numbers and also from trials not designed to assess dose escalation.

The AG's economic model assumed that response included partial response, complete response and stable disease. The response rate to 600mg imatinib was based on a non-comparative sample of 43 patients in arm A (the 400mg arm) who crossed over in the B2222 study[9]. It is worth noting (as mentioned earlier) that the B2222 report only mentions that patients who progressed had imatinib dose increases, without specifying the actual escalated dose.

More importantly, the trials from which these efficacy estimates were extracted were not designed to assess dose escalation and there was no randomisation of patients at the point of disease progression to either dose escalate or remain on imatinib 400mg. This is a significant limitation that was acknowledged by the Appraisal Committee involved with the original TA86 appraisal in paragraph 4.3.8 *'Committee considered that the data on dose escalation were limited because the number of*

patients involved was small, the length of follow-up for these patients was short, and patients were not allocated to dose escalation by randomisation, possibly leading to bias in the results.'

In addition we reiterate that the definition of dose escalation in the studies was unclear. According to the B2231 (a combination of S0033 and EORTC studies) clinical study report, pxxxxxxx xxxx xxxxxxx xx xxxxxx xxxx xxxx xxxxxxxxx xx xxxxx xxxxxxx xxxx xxx xxxxxxxx xx xxxxxxxxx xxxx xx xxxxx xxxxxxxx xxx xx xxxxx xxx xxx[8]. This implies that some patients who may not have rxxxxxxx xxx xxxxxxxxx xxxx xxx x xxxx xxxxxx xxxxxx xxxxxxxxx meaningful benefits were included in the overall survival analysis. The AG rightly concluded on page 90 of the AR that *'there was a dearth of evidence available on the specific population of interest, despite the overall large evidence base on the treatment of GISTs with imatinib or sunitinib. The quality of reporting of dose information in reports of imatinib or sunitinib for GISTs was poor and the data on the population of interest for the studies that were included was non-randomised, non-comparative and therefore observational. Therefore lack of quality data as well as lack of data itself, severely limited both assessments of clinical and cost effectiveness.*'

To put the data limitations into perspective, consider that the base case ICER in the Assessment Report for pathway 2 (imatinib 600mg to imatinib 800mg to sunitinib) is approximately £46,000 per QALY gained. We assume that this is the same pathway used in TA179[10] where the most plausible ICER that the Appraisal Committee accepted was approximately £32,000 per QALY gained (paragraph 4.6 of TA179). The difference between what the Committee believed and this analysis is £14,000. It is plausible to conclude that this differential in the ICER estimate for the same pathway of care might be accounted for by the differences in efficacy estimates in TA179 and the current analyses. The former being based on RCTs and the latter on efficacy estimates derived from non-randomised observational data, which will inevitably lead to misleading results.

Because of the limitations discussed above, the response rate estimates for the 600mg and 800mg imatinib are unreliable and therefore not robust enough to produce credible clinical and cost effectiveness estimates. For that reason, we believe that it would be misleading for the Committee to make a decision on the clinical and cost effectiveness of imatinib 600mg and 800mg in patients whose disease progresses on 400mg dose.

3.4. Probabilities of survival and non-response: sunitinib

The survival and non-response rates for sunitinib were based on patients who had failed imatinib doses that were less than or equal to 400mg.

The point estimates of the probability of survival in the AR were derived from the Schutte et al study[11]. The AG reported that 231 out of 339 patients were still alive after about 12 months and this survival rate was used to calculate the probability of death in the sunitinib arm. Our assessment of the Schutte et al study shows that the 339 patients on which the survival estimate is based had failed imatinib on doses that were less than or equal to 400mg. It is unclear how many patients failed on 400mg. In addition the study did not clarify the definition of imatinib failure or intolerance, and this is necessary to judge the suitability of the population for this review. For the purposes of this review imatinib failure should be ascertained by disease progression whilst on 400mg imatinib. We therefore consider that the estimates of survival for sunitinib may be based on a population that is not relevant to this review and therefore might lead to biased estimates of sunitinib survival in this setting. The fact that this study did not meet the inclusion criteria set out by the AG, shows that the study was potentially not relevant for this review.

The response rates incorporated into the model were derived from pooled response rates from two studies published by Demetri et al 2006[12] and Prior 2009[13]. The pivotal sunitinib trial (Demetri 2006) shows that 80% of patients who were included in that trial had failed imatinib 800mg before entering the trial. The definition of imatinib failure is unclear from the Prior study as it does not specify at what imatinib dose patients were considered to have failed imatinib before switching to sunitinib and it is therefore difficult to confirm the suitability of this population for this review. We restate, as per our original submission, that sunitinib is a third line treatment option and therefore beyond the scope of this review and should not have been a comparator in this appraisal. The AG also agree with this view that sunitinib is a third line treatment (AR page 90).

Furthermore it is unclear from the AR how the indirect comparison of imatinib and sunitinib was conducted, given the differences in the populations and the pooling of

RCT and non-RCT sunitinib data with no common comparator for the two treatments (likely to be BSC, in which case all the limitations highlighted earlier apply).

We thus conclude that the bias introduced by comparing different populations and the uncertainty from the weak indirect comparisons of imatinib and sunitinib, is unsound to base decisions on the cost effectiveness estimates produced in the AR that compare imatinib to sunitinib in the pathway of care.

3.5. Constant transition probabilities over time

The assumption of constant probabilities over time is too simplistic and clinically implausible.

The probabilities calculated for 600mg and 800mg imatinib for death and non-response were assumed to be constant over time i.e. constant probabilities for non-response and death to imatinib 600mg and 800mg for the full model time horizon. This assumption is likely to be clinically implausible and simplistic with an unknown impact. The AG concurs that the assumption of constant probabilities for non-response over time was not plausible as evidenced by the following statement on page 92 of the AR: *'The impact of making alternative assumptions about how probabilities for death and response change is unknown but it is anticipated that the assumption of constant probabilities over time will exaggerate estimated life expectancy (and hence QALYs and cost) for all pathways. The net impact on relative cost-effectiveness is unclear as it depends upon the magnitude of any changes in both costs and QALYs that might occur.'*

We agree with the AG's assessment and we believe that the impact of assuming constant probabilities of death and response generally delays the transition of patients towards death in the model. This is based on the premise that in reality the probability of death increases over time as the disease progresses. Patients also become resistant to treatment, and therefore receive either a higher imatinib dose or sunitinib. On the other hand, it is envisaged that the probability of non-response to treatment (modelled) also increases for similar reasons as highlighted above.

The combined effect of this is to have more patients dying in the model than is currently assumed. If this interpretation holds, it would mean that the current analysis has a bigger impact on the active treatment arms (i.e. imatinib 600mg/imatinib

800mg/sunitinib) because although patients are accruing benefits, they also accrue costs as they survive longer in the model than would otherwise be the case. The true magnitude of this effect is not known but we agree with the AG's conclusion that it may be significant in terms of its impact on costs and QALYs.

3.6. Adverse events

The exclusion of the impact of adverse events in the economic analysis may lead to misleading cost effectiveness estimates.

The AG could not model the effect of adverse events on the clinical and cost effectiveness of imatinib dose escalation due to lack of data. We agree that both imatinib and sunitinib, like all medicines, will have side effects, but sunitinib has a less favourable side effect profile than imatinib (sunitinib SmPC[14] and the AG conclusions on pages 82 and 92 of the AR). Therefore the exclusion of the disutility of side effects in the economic analysis due to lack of adverse events data is likely to favour sunitinib.

The AG agrees with this view and they state that they *'made a simplifying assumption of not modelling the complications and side effects of therapy.'* The AG further state that *'no utility decrement was assumed for the worse side effect profile of sunitinib.'* The AG finally concludes that the *'exclusion of side effects means that pathways involving sunitinib may overestimate QALYs.'* (AR page 91). We fully agree with this view and we believe that the estimates of cost effectiveness reported are misleading partly due to the exclusion of adverse events in the economic analysis and the data issues highlighted earlier.

3.7. Costs

The economic analysis seems to have included some of the costs of managing adverse events in the estimates of cost effectiveness, although the disutility of the adverse events was not incorporated. It is unclear which adverse events these costs relate to and, more importantly, the costs of managing adverse events were assumed to be the same for imatinib 600mg, imatinib 800mg and sunitinib despite clinical evidence as well as the AG's admission that sunitinib has a less favourable side effect profile than imatinib (AR pages 82 and 92). In addition the costs used for adverse events seem to be costs associated with adverse events for first line imatinib

treatment, and not the cost of managing side effects experienced by patients whose disease progresses. It seems inappropriate to assume that the costs of managing side effects for first line treatment will be the same as those for dose escalated patients to a higher imatinib dose. Although it is accepted that these costs are a small proportion of the total costs and might be insignificant in the context of this analysis.

The costs of CT scans for imatinib were sourced from the 2005 HTA monograph[5]. It is not clear from the analysis why the cost of CT scans varied between imatinib and sunitinib (£656 versus £336). The UK clinical guidelines recommend that metastatic GIST patients should have a CT scan every 3 months irrespective of whether they are receiving imatinib or sunitinib[1]. The effect of assuming similar costs of CT scan for imatinib and sunitinib is likely to be insignificant in the context of this analysis but it contributes to the cumulative uncertainties in the cost effectiveness estimates.

3.8. Inconsistencies observed in the Assessment Report

There are a number of inconsistencies identified in the Assessment Report; these are detailed below.

(a) Probability of non-response for imatinib 800mg

The probability of non-response in the imatinib 800mg arm was based on pooled response rates of dose-escalated patients in the S0033[7] and EORTC[6] studies. The calculated probability of non-response for imatinib 800mg in the AG's excel file submitted with the model is 0.012269. However the probability of non-response that was incorporated into the model for imatinib 800mg was 0.012879; the probability of non-response was therefore higher in the model than the calculated rate. When the lower probability is incorporated into the model, there is a marginal improvement in the base case cost effectiveness estimates of the paths involving the 800mg arm. Whilst pointing out this inconsistency we believe that the more important issue is the bias and uncertainty inherent in the data, given that the efficacy estimates were extracted from a trial that was not designed to assess dose escalation and was therefore non-randomised and non-comparative.

(b) Probability of death in the imatinib 600mg arm and probability of survival for sunitinib

The estimate of the probability of survival for the 600mg imatinib dose is based on an estimate of 55% survival at 60 months reported in the B2222 study[9], implying a mortality rate of 45%. The AG reported the mortality rate as 55% (6.05/11) and survival of 45% in the excel file, although it used the correct survival (based on their calculations) of 55% in the exponential formulae. In addition, page 64 of the AR states that 193 out of 351 patients receiving sunitinib were still alive after a median survival of 11.76 months while the model uses 231 out of 339 patients.

(c) Pooled BSC mortality estimates

The BSC survival estimates were calculated from a pooled weighted rate from three studies in table 15, page 66 of the AR. However in the excel file the estimate is based on two studies (Pierie 2001[4] and McGrath 1987[3]). The same file also states that the survival estimate was based on five pooled studies, so it is therefore unclear which studies were pooled to estimate mortality in the BSC arm. We reiterate that the biggest limitation with the studies is their observational, non-comparative nature and more importantly the fact that the population represented in these identified studies is not reflective of the population of interest in this review.

(d) Total costs of path-4 and path-2

Table 16, page 71 of the AR, shows the total costs of paths 4 and 2, where the dominated or extendedly dominated options have been excluded. The total costs for path-4 and path-2 should have been £147,060 and £172,152 respectively, and not £189,484 and £212,595. We believe that this is a typographical error because, on running the model, the correct costs are generated and therefore does not affect the final ICERs that were calculated.

4. Other comments

4.1. Imatinib licensed indication

The AR states that *"Preliminary results from one randomised, placebo controlled phase III trial suggest that adjuvant therapy with imatinib (400mg/day for one year) increases recurrence-free survival following resection, and it is therefore suggested that adjuvant imatinib may have an important role to play in the prevention of recurrence of GISTs after resection..."* (AR Section 3.2.1.1, page 3).

We feel that this statement does not make it sufficiently clear to readers that imatinib is approved for the adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD 117)-positive GIST. Imatinib received a licence in this indication in April 2009[15]. We suggest such clarification is given after this statement or the sentence is amended to reflect the approval status.

4.2. Acquired resistance

On page 5 of the AR is the statement *"Primary resistance to imatinib is uncommon, but acquired resistance is inevitable and manifest clinically by the observation of disease progression."*

The references for this information do not substantiate that acquired resistance is "inevitable". Furthermore we do not believe that any available references support this statement that 'resistance is inevitable' and therefore do not accept that this text is correct.

4.3. Treatment options for unresectable and metastatic GIST

The AR states on page 10 that *"other new treatments for unresectable and/or metastatic GIST have become available, including sunitinib, which has been recommended by NICE as the second line treatment for the population of interest, after failure on treatment with imatinib..."*

We would like to clarify that, to date, imatinib and sunitinib represent the only approved treatment options for this population. Imatinib is the only licensed drug for

first line treatment for unresectable and metastatic GIST[15]. Sunitinib is the only drug approved for the treatment of unresectable and/or metastatic malignant GIST after failure of imatinib treatment due to resistance or intolerance[13]**.** Furthermore within the registration study for sunitinib, the majority of patients were randomised to sunitinib treatment or to the placebo arm after failure of imatinib 600-800mg dose[12].

5. Conclusion

In conclusion, we summarise the limitations of the analysis in the AR as follows:

Clinical evidence limitations

- No relevant clinical data (RCT or non-randomised observational data) exist for patients who were dose escalated after disease progression on 400mg and were treated with best supportive care.
- The efficacy estimates of patients whose disease progressed but were not dose escalated is unknown as they were not followed up. This was the ideal patient group representing patients receiving BSC after progressing on 400mg imatinib dose.
- The BSC population from the three retrospective studies identified by the AG does not seem to match the population of interest in this review. The patient population in these retrospective studies were patients with no confirmed diagnosis of GIST based on the Kit (CD 117) receptor and were patients with resectable gastrointestinal (GI) sarcomas or leiomyosarcomas (LMS).
- There are currently no head-to-head trial data comparing imatinib and sunitinib.
- 80% of patients in the pivotal sunitinib trial had already failed on imatinib 800mg before entering the study.
- The evidence base for imatinib 600mg and 800mg is derived from trials that were not designed to assess dose escalation. Thus patients were not randomised to dose escalate at the point of disease progression.
- The dose-escalated dataset is based on few patients e.g. the survival estimate for the 600mg dose escalated subset is based on a sample of 11 patients.

- The definition of dose escalation is unclear and the studies indicated that patients were defined as dose escalated if they received hxxxxx xxxxx xxx xx xxxxx x xxx.
- The actual dose that dose-escalated patients received is unclear. For example the B2222 study does not state to which dose patients were escalated to, but only mentions that they were escalated to a higher imatinib dose.
- There were no data to assess the efficacy of imatinib dose escalation in patients with specific gene mutations

Economic evaluation limitations

- There is considerable uncertainty in the extrapolation of point estimates of efficacy based on potentially biased data and few patients into a lifetime horizon in the model.
- Generally the economic analysis is based on sparse data that are prone to significant bias and considerable imprecision.
- The assumption of constant probabilities of death and non-response might not be clinically plausible and may have an impact on estimated costs and QALYs.
- Due to lack of data the impact of the disutility of adverse events, especially on sunitinib, was not incorporated although the costs of managing certain adverse seem to have been included in the analysis
- There was a lack of quality of life outcomes on patients who progress on 400mg imatinib, and the health state utilities used were based on patients who were treated with 400mg imatinib and not patients who were dose escalated on disease progression.

As can be seen in the summarised points above, the available data were too flawed or were based on patient numbers that were too low to allow the construction of a robust economic analysis. The data that were used in this analysis exhibit a number of flaws which cast doubt on the outcomes of the AR.

We believe that in this instance the economic evaluation is subject to a high level of uncertainty due to the paucity of data and is not robust enough for the Committee to make an informed decision about the cost effectiveness of imatinib dose escalation for patients whose disease progresses on 400mg imatinib. The AG themselves have

emphasised several times in the assessment report that the cost effectiveness results should be treated with caution because of the cumulative effects of the limitations as discussed.

Although clinical practice has evolved to include dose escalation on disease progression to the benefit of patients as we highlighted earlier, there is a lack of clinical data to support a robust health economic case for this patient group.

In summary, the economic analysis conducted by the AG has been severely hampered by the paucity of data in this relatively discreet and small population. Consequently there is insufficient evidence on which to base an update to the current recommendations. We therefore recommend that the Appraisal Committee considers issuing a recommendation reminder for TA86 rather than issuing new guidance.

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