17th May 2010

PFIZER response to:

NICE Appraisal: Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours (part review of TA86)

Technology Assessment Report (TAR)

- Pfizer has reviewed the Assessment Report relating to the clinical and cost-effectiveness of imatinib at escalated doses of 600 mg/day or 800 mg/day for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours (GIST) which have progressed on treatment at a dose of 400 mg/day.

- The data supporting the use of escalated doses of imatinib is limited and difficult to interpret in the context of managing patients following progression. Moreover, no data on overall survival (OS) for imatinib 600 mg/day were found in the review of clinical effectiveness. Nevertheless, we acknowledge that in clinical practice the majority of clinicians will use an escalated dose of imatinib following progression on the 400 mg/day dose.

- Sunitinib is indicated for the treatment of unresectable and/or metastatic malignant GIST after failure of imatinib mesilate treatment due to resistance or intolerance. Recent NICE guidance recommends sunitinib within this license indication based on the results of a phase III RCT *(NICE, TA179*).

- The phase III RCT evidence includes patients who have progressed on all doses of imatinib (*Demetri et al. 2006*). The majority of patients in the RCT progressed on treatment with the escalated doses of imatinib (>400 mg/day). However, Demetri et al present a subgroup analysis by previous imatinib dose (≤400 mg/day versus >400 mg/day) and conclude that the benefits of sunitinib on time to tumour progression were independent of the dose of initial imatinib treatment.

- Pfizer are very concerned that the evidence used for sunitinib within the TAR is based on data taken from an expanded access programme (EAP) rather than the phase III RCT. The EAP constitutes a single-arm, observational study where, importantly, patients were only included if they were ineligible for the phase III RCT (*Seddon et al. 2008*). Evidence for sunitinib from the EAP will not therefore be comparable to the other data sources for imatinib or best supportive care (BSC) derived from RCTs.

- We conclude that the evidence included for sunitinib within the TAR is suboptimal versus the phase III RCT for decision making. This is particularly the case with respect to the appropriateness of treatment following progression on the escalated doses of imatinib. Further, the clinical and cost-effectiveness conclusions within the TAR may lead to misunderstanding and confusion versus the existing results and recommendations within NICE TA179 based on the phase III RCT.

- Pfizer maintain that the direct evidence from the phase III RCT versus BSC should be used as an alternative to indirect comparisons between the EAP and BSC from non-comparable trials. Further, we emphasise that pathways in the economic model including sunitinib following escalated doses of imatinib (pathways 2, 3 and 5) are outside of scope for the appraisal objectives and are more robustly addressed already within TA179.

The specific limitations in relation to the clinical and cost-effectiveness of sunitinib in this setting are as follows:

Clinical-effectiveness

- There are currently no head-to-head trial data comparing imatinib high dose with sunitinib.

- The included sunitinib observational study (*Seddon et al. 2008*) does not meet the inclusion criteria for this appraisal for the following reasons:

  This sunitinib trial referred to in the review is an expanded access programme (EAP) that involved more than 1000 patients and was initiated to provide pre-registration access to sunitinib and to obtain safety and efficacy data from a large, broad GIST population, reflective of clinical practice. There was no control arm in the trial, hence the relative benefit of sunitinib versus any other treatment is unknown.

  The inclusion criteria for the EAP should not be compared with the more rigorous and strict approach taken in RCTs such as those for imatinib. In particular, only patients ineligible for the pivotal phase III sunitinib RCT were included.

  Out of five included studies, the sunitinib trial was the only observational study that did not have comparative data of escalated doses of imatinib (600mg/day or 800 mg/day).

  The trial was not designed to assess the effects of dose escalation in patients with advanced and/or metastatic GIST whose disease had progressed on the 400 mg/day dose. In fact, the trial had not planned any formal hypothesis testing. The number of patients to be enrolled was not predetermined and no inferential analyses were planned due to the nature of this study. Furthermore, it is not known whether the patients highlighted by the TAG (n=351) had entered the trial due to resistance and/or intolerance and so the data are open to bias.

  The reported trial results were immature with 50% of patients were still alive at the data cut-off point.

- Of considerable concern was the data used to inform overall survival for imatinib 600 mg/day. The clinical effectiveness section found no median OS results for imatinib 600 mg/day. Nonetheless the economic model incorporated a survival estimate of 5 out of 11 patients who crossed over to imatinib 600 mg/day in phase II trial. This data predicted greater overall survival than imatinib 800 mg/day, illustrating the limitations of the data and the economic modelling approach. This data seems unfit to support the model results for imatinib 600 mg/day.

- We would question the validity of the "cross design" approach that was utilised in comparing sunitinib vs. escalated dose of imatinib 800 mg/day. Out of the total 1, 117 patients participating in the study, only 351 patients received sunitinib following progression on ≤ 400 mg/day. Of these 193 (55%) patients were still alive at the time of the OS analyses. Thus, Seddon et al. is likely to underestimate overall survival of the patients. For this reason and other design issues mentioned above we believe that sunitinib trial was not comparable to Blanke et al. even after using meta-analysis models to adjust for study type.

- Evidence available for sunitinib was very poor, with the decision-making process having to be based on observational study evidence without a simultaneous comparator. We agree with the conclusion of the TAG:

  "The included studies were essentially observational in nature and subject to the biases associated with such data, consisting mostly of reporting of subgroups of patients who had been enrolled in RCTs that were not designed to assess the effects of dose escalation on patients with advanced and/or metastatic GIST whose disease had progressed on the 400

mg/day dose. Therefore the selection of patients was neither randomised nor consecutive (p. xiv)".

"…. such data are potentially biased, with both the magnitude and direction of the bias being uncertain. Therefore, all results should be interpreted with caution (p.xiii)".

Economic Model

- Based on a review of the economic model, we would like to draw attention to the substantial limitations in the data inputs utilised, which reflect the paucity of good-quality studies identified in the systematic review, as well as to the limitations of the modelling approach itself. As the TAG points out:
  "*Few data were available for any of the treatments, little of which was based on direct comparisons. Therefore, the data available are imprecise and potentially biased…"*

  Limitations of the data cited in the economic model report include the following key areas:

The base case analysis predicted that treatment with sunitinib was expected to have a lower life-expectancy than best supportive care. Of substantial concern was the fact that the economic model predicted a better overall survival result for BSC than sunitinib. As the TAG points out *"the estimates of survival for sunitinib were based upon limited non-randomised and non-comparative data (as was the case for all the other comparators). Hence any comparison should be treated cautiously."* This result is contrary to the accepted body of evidence supporting the superior efficacy of sunitinib in GIST (see *NICE, TA179*) and illustrates the substantial limitations of the included data and modelling approach.

- Due to the admittedly limited data available for imatinib 600 mg/day and imatinib 800 mg/day, the base case analysis assumes greater effectiveness in terms of OS for imatinib 600 mg/day than imatinib 800 mg/day. While sensitivity analysis attempts to explore the impact of this inconsistency, this illustrates the lack of comparability of the included source data.

The model assumed that the probabilities of progressing and dying did not change over time (made based on limited data availability). A more robust analysis would test a number of assumptions around the rate of change of the hazard ratio. Based on precedent from a number of NICE decisions in oncology we feel that this approach lacks methodological rigor and is a potential key weakness of the approach taken.

- Additionally, further simplifying assumptions made by the model (including treatment pathways, utility values, lack of consideration of adverse events) further illustrate the lack of good-quality inputs available and represent additional limitations of the modelling approach taken.

- We also agree with the uncertainties suggested by the TAG, particularly the point regarding the effects of dose modification and potential effects of sunitinib for both the population being given this drug because of intolerance to imatinib and those receiving sunitinib after failure.

- The limitations of this non-randomised, open-label, non-comparative data used to populate this model mean that the comparability of the different treatments is limited and unreliable. Without higher quality data based on head-to-head RCTs, or a methodologically rigorous mixed treatment comparison of RCT data, the comparative efficacy of treatments is uncertain. This lack of good-quality data inputs, along with the many simplifying methodological assumptions made, draw into question the reliability of the cost effectiveness analysis results.

Summary

Based on the review and the points raised above, Pfizer would again like to raise its concern at the clinical and cost-effectiveness results presented for the use of sunitinib. Whilst the TAG have gone to appropriate lengths to point out the many limitations, biases, and uncertainties relating to the modelling and data used, we are concerned that should these analyses be incorporated in to guidance, this could lead to significant misinterpretation and confusion amongst healthcare professionals and patients alike. We are particularly concerned about the reference to the cost-effectiveness of sunitinib vs. BSC which seems to suggest a poorer survival outcome in the sunitinib arm, despite the data from the EAP which suggest a survival of 90 weeks in patients who have failed 400mg/day. This appears contrary to the evidence supporting sunitinib in the current NICE guidance and phase III RCT. Although the TAG have attempted to explain this result, it remains unclear and could be misleading.

Factual inconsistency:

Page 5, last paragraph: It should read …multicentre phase III trial [and not phase II trial].