THE CLINICAL AND COST-EFFECTIVENESS OF SUNITINIB FOR THE TREATMENT OF GASTROINTESTINAL STROMAL TUMOURS: A CRITIQUE OF THE SUBMISSION FROM PFIZER

Review of Pfizer's response to the NICE ACD

Report commissioned by: NHS R&D HTA Programme
On behalf of: NICE
Produced by: Peninsula Technology Assessment Group (PenTAG)

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This addendum is in reply to the response from Pfizer (received March 2009) on the NICE ACD.

Abbreviations & Acronyms reminder:
OS = Overall Survival
BSC = Best Supportive Care
RPSFT = Rank preserved structural failure time method
ITT = Intention to treat
TTP = Time to Tumour Progression

End of Life
Here, we do not comment on whether sunitinib for GIST should be considered under the terms of NICE's guidance for "End of Life". Instead, we comment on Pfizer's discussion of sunitinib in the context of End of Life (p1 Pfizer's response).

- Pfizer state that OS for BSC under the RPSFT method is 39 weeks. We presented the mean OS for BSC under the RPSFT method as 1.21 years = 63 weeks (Table 20, p78, PenTAG report). This was the value calculated by Pfizer in their original submission. This value is still lower than the 2 years necessary for categorization as End of Life. Under the ITT method, the mean OS for BSC is 1.79 years (Table 21, p79, PenTAG report), also lower than the 2 years necessary for categorization as End of Life.

- We agree with Pfizer's value of an additional 9 months OS for sunitinib versus BSC, assessed using the RPSFT method (Table 20, p78, PenTAG report). Under the ITT method, the additional OS is 0.19 years = 2.3 months (Table 21, p79, PenTAG report), which is lower than the 3 months threshold for End of Life.

Results: Table 1
We agree with the figures in the results Table 1, except the probabilities that sunitinib is cost effective, see below. The first cycle of sunitinib is assumed free of charge to the NHS.

1) Rank Preserved Structural Failure Time method
We have no factual disagreements with Pfizer's defence of their use of the RPSFT method (p3-4, and Appendix 2 of Pfizer's response).

Pfizer highlight a sensitivity analysis we performed: fitting a Weibull curve to the sunitinib OS Kaplan-Meier data and using the reciprocal of the hazard ratio to derive the BSC OS curve, yielding an ICER of £25,783 / QALY. We and Pfizer both do <u>not</u> advocate this method for the base case. Instead, we agree with Pfizer that Weibull curves for BSC and sunitinib should be fitted independently.

2) Cost of acquisition of sunitinib in progressive disease

Pfizer state (p5 their response): "Although 22% of sunitinib patients within the clinical trial remained on treatment beyond disease progression, there is insufficient evidence to understand whether this would happen within clinical practice." This seems reasonable. However, we think that the cost of acquisition of sunitinib in progressive disease should be included in the economic model base case so that treatment costs are consistent with the trial clinical outcomes. To illustrate this point, if treatment with sunitinib had not been given to patients in progressive disease, it is possible that patients in the sunitinib treatment arm would have died sooner.

Pfizer estimate the additional cost of sunitinib in progressive disease as £2,229 versus our estimate of £2,237. Given that this difference is so small (0.4%), we have not investigated the cause of this discrepancy.

We agree with (to within £100 or £200 / QALY) all the ICERs calculated by Pfizer in their Table 3, and we agree with the breakdown of costs and QALYs in Pfizer's Table 1. We emphasise that focus should remain on the ICER of £31,817 / QALY since this reflects the use of sunitinib in progressive disease actually experienced in the RCT.

3) Expanded Access protocol

The Weibull parameters cited in Appendix 1 of Pfizer's response yield PFS and OS curves for sunitinib that correspond well to the TTP and OS curves from the Expanded Access trial (which are shown in Figure 6, p56 of our original report). Therefore, although we have not formally fitted Weibull curves to the Expanded Access Kaplan-Meier curves, we are satisfied that the curves that Pfizer have fitted are reasonable. Using Pfizer's Weibull parameters, we agree with two of the ICERs Pfizer have quoted in Table 5 of their response: the £47,628 / QALY taking PFS and OS for sunitinib from the Expanded Access trial, and taking PFS and OS for BSC from the RCT (as in the base case), and the £47,102 / QALY taking only PFS for sunitinib from the Expanded Access trial, with all other survival curves from the RCT. This last ICER of £47,102 / QALY is very similar to the value of £46,300 / QALY that we quoted in our original report (p93). We have not checked the other ICERs Pfizer have quoted in their Table 5 due to time constraints and because we judge these figures to be of secondary importance.

4) Censoring patients at cross over

Assuming that the Kaplan-Meier data for patients censored at cross-over (Figure 3, Pfizer's response) is correct, we agree with Pfizer that any cost-effectiveness analysis based on patients censored as cross-over should be considered as suggestive only. This is because the Kaplan-Meier curve in Figure 3 shows that the number of patients at risk who are censored at cross-over is very small after about 4 months, indicated by the very long drops in the Kaplan-Meier curve at 10 and 40 months. This means that the Kaplan-Meier curve is only accurate for follow-up up to about 4 months, which is clearly inadequate for the long-term estimation of overall survival for BSC.

Pfizer have not described how they fitted a Weibull curve to the Kaplan-Meier curve for patients censored at the time of cross-over (thus yielding parameters given in

Appendix 1 of their response). However, we assume that they used the same method as they described in their original submission, namely fitting one survival data point per month throughout the full length of the Kaplan-Meier curve. If so, we suggest that this method is unreliable in this case, due to the very low numbers of patients at risk from 4 months onwards. Without the availability of individual patient data, we would have fitted a Weibull curve to just the first 4 months of the Kaplan-Meier curve, where more patients are at risk. This probably would have yielded worse expected overall survival for BSC, and therefore a more favourable ICER for sunitinib versus BSC. Furthermore, the very long median BSC OS of 156 weeks quoted by Pfizer is highly unreliable due to the very small population at risk at this time.

However, we believe that such short follow-up for patients randomised to BSC before cross-over highlights the great reliance that is placed on the RPSFT method in adjusting the overall survival of these patients. Nonetheless, as Pfizer state on p18 of their response, the OS hazard ratio from the interim analysis, 0.491, which was less confounded by crossover, is similar to the hazard ratio from the RPSFT method, 0.505. This gives some support to the validity of the RPSFT method.

We agree with Pfizer that there were only about patients 15 patients who did not cross over from BSC to sunitinib. We also agree with Pfizer that we should give very little credence to a cost-effectiveness analysis based on this patient group, because there are so few patients, and because that this may represent a select patient group. Therefore, we suggest that very little importance should be attached to Pfizer's results in Table 6 of their response, in particular the ICER of £20,618 / QALY.

5) Probabilistic sensitivity analysis

We now describe the changes Pfizer have made to their probabilistic model in response to our criticisms (p89-91 our report);

- In our original report, we said that Pfizer have not incorporated all the uncertainty in the treatment effectiveness. In particular, they did not allow for the very large degree of uncertainty in the difference in overall survival between sunitinib and BSC. Pfizer have now allowed for uncertainty in PFS and OS by modelling the published uncertainty in the hazard ratios for PFS and OS. They have implemented this correctly in their model. This approach now departs from Pfizer's base case of fitting survival curves independently for sunitinib and BSC, and thus the deterministic ICER corresponding to their PSA (based on the hazard ratio approach), at £15,600 / QALY (see Table 22, p80 our original report), is much lower than their deterministic base case ICER (based on fitting curves independently for sunitinib and BSC) of £27,365 / QALY. This therefore introduces a bias in the PSA results, namely Pfizer's probabilities that sunitinib is cost-effective are too high. However, having said that, we do not criticize Pfizer, because we know of no other way of modelling the important uncertainty in treatment effectiveness.

- Pfizer have corrected the errors in the uncertainty of the fits of the Weibull curves to the Kaplan-Meier data.

- Pfizer now correctly use the standard errors, not the standard deviations for the uncertainty in the utilities. They have assumed a sample of 196 utility estimates for patients in PFS on sunitinib, 96 utility estimates for patients in PFS on BSC, 14 estimates for patients in PD on sunitinib, and 4 estimates for patients in PD on BSC. The 196 and 96 estimates represent the number of patients surveyed during the double blind phase of the RCT (data from Pfizer from our earlier request). We are unable to check the sample size in PD.

- Pfizer have corrected the standard deviation for the utility in PFS from 0.02 to 0.20.

- In their original submission, Pfizer modelled no uncertainty in the relative dose intensity of sunitinib, mean of 88.6%. They now allow for a small amount of uncertainty in the relative dose intensity, standard error of 1.2%. We have no way of checking the validity of this level of uncertainty.

Pfizer quote the probabilities that sunitinib is cost-effective compared to BSC in Table 1 of their response. They state that the probability that sunitinib is cost-effective assuming no sunitinib use in progressive disease is about 17% and 58% at willingness to pay thresholds of £20,000 and £30,000 / QALY respectively (using the RPSFT method). These values become 8% and 43% assuming sunitinib use in progressive disease. In Table 1, they state that these values are based on modelling uncertainty in the PFS and OS hazard ratios. However, we were unable to recreate these probabilities using their model with this method. Instead, we believe that the probabilities quoted in Table 1 are based on fitting PFS and OS Weibull curves to sunitinib and BSC independently, which, as stated above, allows for very little of the large uncertainty in treatment effectiveness.

When we use Pfizer's model, but allow for uncertainty in the treatment effectiveness via uncertainty in the PFS and OS hazard ratios, as Pfizer intended, we find the probability that sunitinib is cost effective in the base case as 63% and 77%, assuming willingness to pay thresholds of £20,000 and £30,000 / QALY (using the RPSFT method). Now, including the cost of sunitinib in progressive disease, these values become 50% and 70%. However, as stated above, these values are biased too high. Furthermore, we are aware of no superior method to correct for this bias.

As mentioned in our original report, cost-effectiveness is uncertain, mostly due to the large uncertainty in the hazard ratio for OS under the RPSFT method: 95% confidence interval (0.262 – 1.134). Even at the high willingness to pay threshold of £80,000 / QALY, there is still a 10% chance that sunitinib is <u>not</u> cost-effective assuming either no cost or some costs of sunitinib acquisition in progressive disease. Again, this figure is biased: the true probability is greater than 10%.