Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Imatinib for the adjuvant treatment of gastrointestinal stromal tumours

ERRATUM with replacement pages

1st May 2014

This document contains erratum in respect of the ERG report following the factual accuracy check by Novartis

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Authors Jeremy Jones
Petra Harris
Jonathan Shepherd
Keith Cooper

SUMMARY

Scope of the manufacturer submission

This appraisal topic is a review of TA196 'imatinib for the adjuvant treatment of gastrointestinal stromal tumours'. The scope of the submission was in line with the NICE scope, that is to assess the clinical and cost-effectiveness of imatinib as an adjuvant treatment for adults who are at significant risk of relapse following resection of c-KIT (CD117)-positive gastrointestinal stromal tumour (GIST) and in line with the significant risk population in the marketing authorisation. The comparator is observation after surgery (no adjuvant therapy). The TA196 guidance was based on mainly one trial comparing 1-year of adjuvant imatinib with placebo (the ACOSOG Z9001 trial). At that time the NICE Appraisal Committee were aware of on-going clinical trials and this review of TA196 includes the longer-term evidence in the appraisal of the clinical and cost-effectiveness of imatinib.

Summary of submitted clinical effectiveness evidence

The manufacturer's submission (MS) for the clinical effectiveness evidence to NICE included:

i) a systematic literature review to identify all studies reporting on the clinical effectiveness and safety of imatinib in the adjuvant setting of GIST.
ii) three randomised controlled trials (RCTs) (the ACOSOG Z9001 trial, the SSGXVIII/AIO trial, and the EORTC 62024 trial). One RCTs is only available as an interim analysis reported in a conference abstract (EORTC 62024).
iii) twelve non-RCTs of varying relevance to the decision problem, with some failing to report the risk category of the included patients and some failing to report a classification system for the reported risk categories.

Meta-analysis was not performed and would not have been feasible due to methodological differences between the included RCTs (and between the RCTs and non-randomised studies). An indirect comparison of two of the RCTs was conducted to inform the economic analysis.

The population and the comparisons of the three RCTs varied. The ACOSOG Z9001 trial compared 1-year of adjuvant imatinib therapy following surgical resection against placebo, based on patients at any level of risk of recurrence (the trial was conducted prior to the introduction of risk categorisation). The SSGXVIII/AIO trial compared 1-year of adjuvant imatinib therapy following surgical resection with 3-years therapy based on patients with a high

risk of recurrence of GIST (based on modified US National Institutes of Health NIH Consensus Criteria). The EORTC 62024 trial compared 2-years of imatinib therapy following surgical resection with observation only (no treatment) based on patients with intermediate or high risk GIST (based on NIH Consensus Criteria). The SSGXVIII/AIO trial and EORTC 62024 trials were open-label.

The submission provides treatment effect estimates for the full trial populations (intention to treat, ITT) and retrospectively analysed high risk sub-populations. The Miettinen risk classification scheme was used in preference to other classification schemes as this is recommended by UK clinical guidelines.

All three RCTs reported longer recurrence free survival (RFS) associated with adjuvant imatinib treatment. In the ACOSOG Z9001 trial 1-year imatinib compared to no adjuvant treatment was associated with longer RFS at 5-year follow-up (full population HR 0.718 (95% CI 0.531 to 0.971); p =0.0305; Miettinen high risk sub-population: HR 0.608 (0.417 to 0.886; p = 0.009), while in the SSGXVIII/AIO trial 3-year imatinib treatment was significantly associated with longer RFS compared to 1-year treatment at 5-year follow-up (full population: HR 0.46; 95% CI 0.32 to 0.65; $p < 0.0001$; Miettinen high risk sub-population: HR 0.43; 95% CI 0.30 to 0.62; $p < 0.001$). The EORTC 62024 trial showed a difference between imatinib (84%) and no adjuvant treatment at 3-years (66%) in RFS, but similar results at 5-years (69% vs 63%, respectively) (based on interim data and caution is advised in the interpretation of these results).

The results for overall survival (OS) across the two trials which reported this outcome were mixed. The ACOSOG Z9001 trial had few deaths overall and there was no statistically significant difference between 1-year treatment and no adjuvant treatment (full population only: 2-years HR 0.66; 95% CI 0.22 to 2.03, p = 0.47; 5-years HR 0.816; 95% CI 0.488 to 1.365; p = 0.4385). The SSGXVIII/AIO trial (relatively smaller, but evaluating a longer treatment period), reported comparatively more deaths and at 5-years follow-up there was a statistically significantly longer OS associated for 3-years imatinib treatment compared to 1-year treatment (full population: HR 0.45; 95% CI 0.22 to 0.89; p = 0.019; Miettinen high risk sub-population: HR 0.39; 95% CI 0.19 to 0.79; p = 0.007). Differences between the two trials in terms of patient characteristics or other variables may explain the differences in the overall death rates seen. However, neither of the trials was statistically powered for OS and caution is necessary in the interpretation of the results. The EORTC 62024 trial reported imatinib-failure-free survival (IFS;

the full populations, indicating selection bias. These sub-populations are most likely underpowered for RFS and OS, though results were not significantly different between the full trial population and the high risk sub-populations (confidence intervals did not cross 1).

The manufacturer states that patients classified as at moderate risk of recurrence are not included in the submission because evidence for this sub-population is less developed, and because there is uncertainty in the prognosis for patients at 'intermediate' (moderate) risk. The ERG notes that there is an unspecified proportion of patients in the ACOSOG Z9001 that would be classified as at moderate risk, but there would be only a small proportion of patients in the SSGXVIII/AIO trial that could be similarly classed as moderate.

The results of the ACOSOG Z9001 trial are confounded by the high degree of cross-over to imatinib by recurrence-free placebo patients when the study became unblinded. The results of the placebo arm of this trial are used as a baseline for comparison to adjuvant imatinib in the manufacturer's economic model. Following the main submission document the manufacturer submitted to NICE and the ERG a supplemental report using various statistical methods to adjust for patient cross-over in the trial. These methods have advantages as well as limitations in terms of assumptions made and their applicability to the trial, and all produced RFS and OS estimates that were lower (to varying degrees) than the ITT analysis and therefore more favourable to imatinib. The manufacturer's favoured method produced HRs that are similar to a per protocol analysis that simply censors switchers at the time of cross-over, and that both of these approaches give HRs that were only slightly lower than the ITT analysis. These results are not formally incorporated into the manufacturer's assessment of cost-effectiveness. It is likely that adjustment of the treatment effects for cross-over would lower the ICERs.

The EORTC 62024 trial currently only provides limited interim results. In common with the ACOSOG Z9001 trial, this study provides a direct comparison with no adjuvant treatment but over a longer-time period (2-years). Data from this study, if fully available, would obviate the need for an indirect comparison with no adjuvant treatment (though it would only be for a 2-year and not a 3-year treatment period), and would potentially not be subject to the limitations of patient cross-over seen in the ACOSOG Z9001 trial.

None of the RCTs identified in the clinical effectiveness systematic review were conducted solely in the UK and the applicability of the evidence to NHS practice and to the UK GIST

Recurrence-free survival/ risk of recurrence for patients undergoing surgery with adjuvant imatinib - off-treatment hazard ratios

Estimation of the off-treatment hazard ratios for 1-year and 3-year adjuvant imatinib required further manipulation of the trial datasets. The first stage (described in the MS as "estimating the Kaplan-Meier curves for the post-treatment phase") involved removing all patients who experienced recurrence or were censored during their planned duration of adjuvant imatinib in both trials. This provided a dataset for, post-treatment, recurrence-free survival for patients who were recurrence-free at the end of their planned duration of adjuvant treatment. The data were not truncated for patients who underwent surgical resection with no adjuvant treatment.

Off-treatment hazard ratios were estimated using these new, derived datasets and are defined in the MS as HR1 (1-year adjuvant imatinib vs placebo) and HR2 (3-year adjuvant imatinib vs 1-year adjuvant imatinib). The values estimated for HR1 and HR2 were 0.519 (95% CI 0.297 to 0.906) and 0.663 (95% CI 0.392 to 1.123).

The off-treatment hazard ratio for 3-year adjuvant imatinib vs placebo (HR3) was calculated using a standard adjusted-indirect comparison method (see below), although the MS contained a documentation error regarding the calculation of the adjusted-indirect comparison. The ERG requested clarification regarding this and were informed that, due to the need to change the reference category for HR2 (to be 1-year adjuvant imatinib vs 3-year adjuvant imatinib) the inverse (1/0.519) was used in the calculation (see clarification request B5).

$$\ln(HR3) = \ln(HR2) - \ln(HR1)$$

$$SEln(HR3) = SEln(HR1)^2 + SEln(HR2)^2$$

where ln() natural logarithm and SEln() indicates the standard error of the natural log.

Using this corrected calculation the hazard ratio for 3-year adjuvant imatinib vs placebo (HR3) gives a value of 0.344 (95% CI 0.160 to 0.741).

Recurrence-free survival/ risk of recurrence for patients undergoing surgery with & without adjuvant imatinib – summary and estimated survival curves

Figure 5 shows the Kaplan-Meier curves and fitted survival functions (using the Gompertz function) for surgery with no adjuvant therapy (ACOSOG Z9001 placebo arm), surgery with 1-year adjuvant imatinib (ACOSOG Z9001 imatinib 12 months arm) and surgery with 3-years of adjuvant imatinib (SSGXVIII/AIO imatinib 36 months arm) derived using the methods described

patients deem unacceptable in the adjuvant setting maybe more acceptable when offered the same treatment for disease recurrence. However it is not certain that all patients will accept the same treatment.

Recurrence and probability of discontinuation in patients receiving non-adjuvant imatinib

The probability of discontinuation due to recurrence in patients receiving imatinib for primary recurrence following surgery is based on the proportion of treatment failures due to disease progression reported by Verweij and colleagues.[45] This trial was conducted between February 2001 and February 2002 in 13 countries with eligibility criteria reported in Table 20. Patients in the trial were randomised (473 in each arm) to receive the standard dose of imatinib (400 mg) either once or twice daily. Verweij and colleagues[45] report that, at 2-years of follow up, 56% of patients randomised to receive 400 mg imatinib once daily experienced treatment failure (consisting of 53% progression and 3% being deaths by any other cause). The equivalent figures for patients randomised to receive 400 mg imatinib twice daily were 48%, with 44% due to progression and 4% deaths from other causes.

The MS states that the monthly probability of discontinuation due to progression is based on the value for imatinib once daily. The calculation is based on a reported value of 44% (which does not agree with the value for imatinib once daily reported by Verweij and colleagues) and yields an estimated value of 0.034 (annual rate (r) = -1/2*ln(0.44), converted to a monthly transition probability as 1-exp(-r/12)). This calculation over-estimates the progression probability and would lead to a modelled discontinuation proportion (in the absence of other transitions) of 56%. Calculating the annual rate correctly for this proportion (-1/2*ln(1-0.44) = 0.290) and converting this to monthly transition probability gives an estimate of 0.024. However, as noted above the progression proportion (44%) used in the MS appears to relate to imatinib twice daily. Using the proportion reported Verweij and colleagues[45] for imatinib once daily gives a monthly transition probability of 0.031 (1-exp(-(-1/2*LN(1-0.53))/12)). Given the small difference between this final value and that applied in the original submission this is likely to have minimal impact on the cost effectiveness results.