

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Topotecan for the treatment of relapsed small-cell lung cancer

1 Guidance

1.1 Oral topotecan is recommended as an option only for people with relapsed small-cell lung cancer for whom:

- re-treatment with the first-line regimen is not considered appropriate **and**
- the combination of cyclophosphamide, doxorubicin and vincristine (CAV) is contraindicated (for details of the contraindications to CAV see the summary of product characteristics for each of the component drugs).

1.2 Intravenous topotecan is not recommended for people with relapsed small-cell lung cancer.

1.3 People currently receiving oral topotecan who do not meet the criteria specified in 1.1, or people receiving intravenous topotecan should have the option to continue their treatment until they and their clinicians consider it appropriate to stop.

2 Clinical need and practice

2.1 Lung cancer can be categorised into four major cell types: small-cell lung cancer, squamous-cell carcinoma, adenocarcinoma and large-cell carcinoma. The last three types are usually described as non-small-cell lung cancer. Small-cell lung cancer grows rapidly and spreads quickly to distant sites (metastasises). It is classified using a two-stage system. The first is limited-stage disease, in

which the disease is generally confined to one side of the chest or to the neck lymph nodes. The second is extensive-stage disease, in which the disease has spread outside one side of the chest and there are systemic metastases. The 'tumour node metastases' stage scores are not usually relevant in small-cell lung cancer because of the high proportion of patients presenting with metastases and the poor prognosis associated with the disease.

2.2 Lung cancer is one of the most common cancers in England and accounted for 15% of cancers in men and 11% of cancers in women in 2005. In England and Wales there were 33,181 new cases of lung cancer in 2005. The disease accounts for around 33,000 deaths per year. It is estimated that small-cell lung cancer makes up about 10–20% of the total cases of lung cancer, but this percentage is falling. The reasons for this are unclear, but changing smoking habits and a reduction in the tar content of cigarettes may be involved. At diagnosis, about 33% of people with small-cell lung cancer have limited-stage disease, but the majority of people have extensive-stage disease.

2.3 In most patients the disease is symptomatic on presentation. In some patients there are non-specific symptoms such as fatigue, loss of appetite and weight loss, while in others there are more direct symptoms such as breathlessness, chest discomfort and haemoptysis (blood-stained sputum). The risk factors for lung cancer include smoking, passive smoking, occupational exposure to asbestos, radon, chromium or nickel, male gender and chronic lung disease. Smoking is the leading cause of lung cancer, accounting for approximately 80–90% of cases. Smoking has been shown to be much more strongly linked to small-cell lung cancer than non-small-cell lung cancer.

2.4 The prognosis for people with small-cell lung cancer is poor. Without treatment, it has an aggressive clinical course with a life

expectancy of approximately 3.5 months for limited-stage disease and 6 weeks for extensive-stage disease. The median survival with treatment is approximately 14–18 months for limited-stage disease and 9–12 months for extensive-stage disease. Approximately 20–40% of patients with limited-stage disease and less than 5% of patients with extensive-stage disease survive for 2 years. Survivors often continue to relapse up to, and occasionally after, 5 years. Prognosis has been linked to performance status and the extent of the disease.

- 2.5 Selection of the most appropriate first-line treatment for small-cell lung cancer is determined primarily by the performance status of the patient and the stage of the disease. Current management of small-cell lung cancer usually consists of combination chemotherapy regimens. Radiotherapy may be given concurrently with chemotherapy or as part of palliative care. Surgery is not appropriate for the majority of patients because the disease is often widespread at the time of diagnosis. For further guidance on the management of small-cell lung cancer, see ‘Lung cancer: the diagnosis and treatment of lung cancer’ (NICE clinical guideline 24).

3 The technology

- 3.1 Topotecan (Hycamtin, GlaxoSmithKline) acts by inhibiting topoisomerase I, an enzyme that is required for DNA replication, leading to cell death. Topotecan is indicated as monotherapy for patients with relapsed small-cell lung cancer for whom re-treatment with the first-line regimen is not considered appropriate. The marketing authorisation for this indication was granted by the European Medicines Agency (EMA) in 2006 for intravenous therapy, and an extension to the marketing authorisation was granted in 2008 for oral capsules.

- 3.2 Adverse effects commonly associated with topotecan include nausea, vomiting, neutropenia, leukopenia, anaemia, fatigue and alopecia. Topotecan is not recommended in patients with severe renal or hepatic impairment. For full details of adverse effects and contraindications, see the summary of product characteristics.
- 3.3 The acquisition cost for intravenous topotecan is £97.65 for a 1-mg vial or £290.62 for a 4-mg vial and for oral topotecan is £30 per 1 mg capsule (excluding VAT, 'British national formulary' [BNF] edition 58). The recommended dose of intravenous topotecan is 1.5 mg/m² body surface area on 5 consecutive days with a 21-day interval between the start of each course. Oral topotecan is administered at 2.3 mg/m² on 5 consecutive days with a 21-day interval between the start of each course. Assuming a body surface area of 1.8 m², the cost per cycle is £1495 for intravenous topotecan and £638 for oral topotecan. Patients in the key clinical trials received intravenous topotecan and oral topotecan for approximately 4 cycles, equating to an average treatment cost per patient of £5980 for intravenous topotecan and £2552 for oral topotecan. Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 Clinical effectiveness

- 4.1.1 The Assessment Group reviewed the clinical effectiveness of topotecan (oral and intravenous) compared with best supportive care or other chemotherapy regimens for the treatment of relapsed small-cell lung cancer. Five randomised controlled trials (RCTs) met the inclusion criteria of the review. The reporting and methodological quality was judged to be good in two trials and

unknown in three trials. The RCTs differed in design and recruited different study populations for topotecan and the relevant comparators. Therefore the Assessment Group considered that it was not appropriate to pool the results.

Oral topotecan compared with best supportive care

4.1.2 One trial compared oral topotecan plus best supportive care with best supportive care alone as a treatment for patients with limited- or extensive-stage relapsed small-cell lung cancer for whom further intravenous chemotherapy was considered unsuitable (n = 141). The primary outcome was overall survival. Quality of life was also measured using the EQ-5D. The median overall survival for patients receiving oral topotecan was 25.9 weeks (95% confidence interval [CI] 18.3 to 31.6) compared with 13.9 weeks (95% CI 11.1 to 18.6) for patients receiving best supportive care alone. The hazard ratio (using Kaplan–Meier analysis) for overall survival was 0.64 (95% CI 0.45 to 0.90) in favour of topotecan plus best supportive care.

4.1.3 EQ-5D data were recorded for each patient in the trial at the start of each cycle (21-day period) up to cycle 12. Individual patient data were available for 600 (39%) 21-day survival periods. The rate of deterioration in the EQ-5D score per 3-month period was –0.05 (95% CI –0.11 to 0.02) for patients receiving oral topotecan plus best supportive care compared with –0.20 (95% CI –0.27 to –0.12) for best supportive care alone. The mean change in EQ-5D score from baseline to the averaged on-treatment assessment (pooled analysis) and the mean change from baseline to the last evaluation showed statistically significant differences between the two groups: –0.03 for topotecan plus best supportive care compared with –0.12 for best supportive care alone (p = 0.0036) and –0.10 for topotecan plus best supportive care compared with –0.30 for best supportive care alone (p = 0.0034), respectively.

- 4.1.4 Rates of non-haematological adverse events appeared to be similar between the two patient groups (statistical significance was not reported). Treatment-related toxicity for the topotecan plus best supportive care arm was reported: 61% of patients had neutropenia that was severe or life-threatening, 3% had febrile neutropenia, 38% had thrombocytopenia that was severe or life-threatening, and 25% had anaemia.

Oral topotecan compared with intravenous topotecan

- 4.1.5 Two trials compared oral topotecan with intravenous topotecan as a treatment for patients with limited- or extensive-stage relapsed small-cell lung cancer who had complete response or partial response to first-line therapy with disease recurrence after 90 days or longer (n = 309 and n = 106). There were no statistically significant differences in overall survival or overall response rates between oral and intravenous topotecan in either of the trials. In the smaller study, the median overall survival for patients treated with oral topotecan was higher than for those patients treated with intravenous topotecan, but the difference was not statistically significant. No statistical analyses of adverse events were reported in either study. Severe or life-threatening adverse events were similar between intravenous topotecan and oral topotecan in the studies, with the exception of neutropenia, which appeared to occur more frequently with intravenous topotecan.
- 4.1.6 The larger of the two studies assessed health-related quality of life using a disease-specific measure, the functional assessment of cancer therapy-lung (FACT-L) scale – a core set of measures with a lung-cancer subscale. In addition the trial outcome index was derived from a subgroup of the data. The mean change from baseline indicated no statistical difference between treatment groups for subscale dimension scores or the lung-cancer subscale, the FACT-L total scores or the trial outcome index.

Intravenous topotecan compared with CAV

- 4.1.7 One trial compared intravenous topotecan with CAV in patients with progressive, limited- or extensive-stage relapsed small-cell lung cancer with the date of progression 60 days or longer after completion of first-line therapy (n = 211). The primary outcomes were response rate and duration of response. An unvalidated, symptom-specific small-cell lung cancer questionnaire was used to measure symptoms of patients in the trial.
- 4.1.8 The median overall survival for patients receiving intravenous topotecan was 25 weeks (95% CI 0.4 to 90.7) compared with 24.7 weeks (95% CI 1.3 to 101.3) for patients receiving CAV. This difference was not statistically significant. The 6-month survival rates were 46.7% and 45.2% for patients receiving intravenous topotecan and CAV, respectively. The 12-month survival rates were 14.2% and 14.4%, respectively (statistical testing was not reported). The results showed an increase in the overall response rate for intravenous topotecan (24.3%) compared with CAV (18.3%) but this difference was not statistically significant.
- 4.1.9 In patients who received intravenous topotecan, greater symptomatic improvement was seen for dyspnoea (p = 0.002), anorexia (p = 0.042), hoarseness (p = 0.043), fatigue (p = 0.032) and interference with daily activity (p = 0.023) compared with CAV. The adverse events reported in the study were similar for the two patient groups, although the incidence of fatigue was lower and the incidence of alopecia was higher in participants receiving topotecan compared with those receiving CAV. No statistical comparison was reported.

Intravenous topotecan compared with intravenous amrubicin

- 4.1.10 One RCT was identified that compared intravenous topotecan with intravenous amrubicin. It was conducted in Japan in patients previously treated with platinum whose disease had relapsed after

completing first-line therapy (n = 59). The primary outcome was overall response rate.

- 4.1.11 The results showed no statistically significant differences in the overall survival for intravenous topotecan compared with intravenous amrubicin (8.4 months and 8.1 months, respectively) or the median progression-free survival (2.2 months and 3.5 months, respectively). Intravenous amrubicin was associated with a statistically significant improvement in overall response rate compared with intravenous topotecan (38% compared with 13%, $p = 0.039$). However, the topotecan dose of 1.0 mg/m²/day (the approved dose in Japan) was below the dose currently being used in the UK (1.5 mg/m²/day). In addition, the study was of an unknown quality because of the lack of details reported in the publication.

4.2 Cost effectiveness

- 4.2.1 Systematic searches conducted by the Assessment Group identified no relevant, published economic evaluations of oral or intravenous topotecan for the treatment of relapsed small-cell lung cancer in patients for whom re-treatment with the first-line regimen was not considered appropriate. Limited information on quality of life or utilities was identified in patients with relapsed small-cell lung cancer. The manufacturer of topotecan submitted an economic evaluation.
- 4.2.2 The aim of the manufacturer's analysis was to compare the cost effectiveness of oral topotecan plus best supportive care with best supportive care alone in people with relapsed small-cell lung cancer for whom treatment with intravenous chemotherapy was not considered appropriate. The analysis was based on patient-level data from the RCT that compared oral topotecan with best supportive care in patients for whom intravenous chemotherapy was not considered appropriate. CAV was excluded as a

comparator from the analysis on the basis that topotecan (oral or intravenous) would not provide a cost-effective alternative to CAV in the majority of patients, because of its higher acquisition cost.

- 4.2.3 The perspective was that of the NHS and personal social services (PSS), and included only the costs and benefits directly relevant to the intervention. The submission stated that costs and outcomes for each treatment arm were estimated over a lifetime horizon. However, survival was not modelled beyond the duration of the trial. Patients who were still alive at final follow-up were assumed to have died the next day.
- 4.2.4 Health-related quality of life was recorded in the study using the EQ-5D, for up to 12 cycles (36 weeks), and valued using a UK general population tariff. Missing values were estimated using data from the trial, using the mean utility score (across both trial arms) for missing values up to cycle 12. When patients receiving topotecan survived with non-progressive disease beyond the 36-week data collection, the last observation was carried forward until disease progression occurred. Once these patients developed progressive disease, values for those receiving best supportive care alone were applied.
- 4.2.5 The costs included in the model were drug acquisition costs, drug administration costs, drug monitoring costs, costs of treating haematological and non-haematological adverse events, and costs of providing care in the additional period of life attributable to oral topotecan combined with best supportive care. Resource use not collected in the trial was taken from clinical opinion. The cost year for the model was 2007–08.
- 4.2.6 In the manufacturer's base case, the incremental life years and quality-adjusted life years (QALYs) gained for the cohort of patients receiving oral topotecan plus best supportive care compared with

those receiving best supportive care alone were estimated at 0.259 life years and 0.211 QALYs gained, respectively. The incremental cost was £5671, giving an incremental cost-effectiveness ratio (ICER) of £21,878 per life year gained and £26,833 per QALY gained.

- 4.2.7 Deterministic sensitivity analysis showed that the results were sensitive to methods of estimating utility (methods of carrying forward utility scores when there were missing data), drug administration cost (significantly higher costs if a patient attended as an outpatient on 5 days of the cycle to receive chemotherapy compared with 1 day of the cycle) and adverse event costs (halving or doubling adverse event costs). Probabilistic sensitivity analyses were also performed.
- 4.2.8 The Assessment Group developed a survival model to estimate the cost effectiveness of topotecan compared with best supportive care in a cohort of adults with relapsed small-cell lung cancer for whom re-treatment with the first-line regimen was not considered appropriate. The model included three states: relapsed small-cell lung cancer (entry to the trial), progressive disease and death. The economic evaluation was a cost–utility analysis and the perspective was that of the NHS and PSS. The outcomes evaluated were life years and QALYs gained over the lifetime of the patients. The base-case model had a 5-year time horizon.
- 4.2.9 The base-case analysis of the model was limited to oral topotecan plus best supportive care compared with best supportive care alone (based on the same study as the manufacturer’s analysis). The Assessment Group also completed an analysis of intravenous topotecan compared with best supportive care, based on an indirect comparison. The Assessment Group had reservations about this analysis given the uncertainty of whether the trials on which the analysis was based fully met the criteria for the review,

the comparability of the patient populations in the RCTs and the suitability of pooling their results.

4.2.10 The model used the published Kaplan–Meier estimates for overall survival and time to progression included in the manufacturer’s submission. The survival curves were extrapolated using a regression analysis (log-logistic survival function). The mean time to progression for oral topotecan plus best supportive care was estimated using an exponential approximation to derive the risk of disease progression from the reported median time to progression, because no Kaplan–Meier estimates for time to progression were reported. The mean time to progression was then calculated to be 23.52 weeks. An adjusted indirect comparison was undertaken to assess the effect of intravenous topotecan on overall survival relative to best supportive care, using data from three RCTs included in the clinical-effectiveness review. The relative risk for overall survival with intravenous topotecan was 0.68 (95% CI 0.45 to 1.02) compared with best supportive care.

4.2.11 The utility values used in the model were those reported for patients in the RCT comparing oral topotecan plus best supportive care with best supportive care alone. This was the only relevant study identified in the Assessment Group’s review of quality-of-life data. EQ-5D scores from the trial were reported as a rate of deterioration per 3-month interval for patients in each arm of the trial, controlling for baseline utility. The baseline utility for all patients in the model was assumed to be 0.7. The reported reductions over 3 months were converted to daily utility reductions (with regression analysis) for use in the Assessment Group’s model and applied to the baseline utility value. The rate of deterioration reported for oral topotecan plus best supportive care was used for patients prior to disease progression. To allow for reduced quality of life in patients following disease progression, the rate of deterioration reported for best supportive care alone was applied to

patients receiving oral topotecan who had experienced disease progression.

- 4.2.12 The resource-use was estimated from the RCTs included in the clinical-effectiveness review, the manufacturer's submission and advice from clinical specialists. When insufficient detail was available (such as for palliative care), appropriate costs were taken from published sources. Drug costs were taken from the BNF, edition 56. Other unit costs were taken from NHS reference costs, Southampton University Hospitals Trust or published sources. The cost base for the evaluation was 2007–08. Costs were adjusted for inflation when taken from other cost years.
- 4.2.13 The addition of oral topotecan to best supportive care resulted in a life-expectancy gain of 0.33 years (approximately 16.9 weeks) and a gain of 0.1830 QALYs. The incremental cost was approximately £6200, resulting in an ICER of £33,851 per QALY gained.
- 4.2.14 Intravenous topotecan was associated with a gain in life expectancy of 0.30 years (approximately 15.9 weeks). The QALY gain associated with intravenous topotecan was between 0.163 and 0.191 and the incremental cost was between £12,060 and £12,514, depending on the assumptions regarding time to progression. The resulting ICER for intravenous topotecan compared with best supportive care was between £74,074 and £65,507 per QALY gained.
- 4.2.15 Compared with oral topotecan, intravenous topotecan was either strictly dominated (worse outcomes at higher cost) or resulted in an ICER of £783,734 per QALY gained, depending on assumptions regarding time to progression.
- 4.2.16 The Assessment Group's survival model gave a higher estimate of mean survival than the manufacturer's model using the patient-level data. This difference was mainly because of the assumption,

in the manufacturer's model, that censored patients die on the day after censoring. The manufacturer and the Assessment Group also used different ways to estimate the utilities in the analysis. The manufacturer used the observed mean EQ-5D scores from the first 12 cycles from both arms of the trial to take account of missing data from the corresponding cycles. When patients receiving topotecan survived with non-progressive disease beyond the 36-week (12 cycles) data collection, the last observation was carried forward until disease progression occurred. Once these patients developed progressive disease, values for those receiving best supportive care alone were applied. The Assessment Group used a regression analysis to estimate the daily rate of deterioration in utility and applied this to the baseline utility values from the RCT comparing oral topotecan with best supportive care, in order to model utility beyond the last observation and beyond the trial. The Assessment Group's base-case ICER was higher than that of the manufacturer for oral topotecan plus best supportive care compared with best supportive care alone (£33,851 and £26,833 per QALY gained, respectively).

- 4.2.17 The Assessment Group did not conduct a formal economic analysis of oral topotecan compared with CAV because of the lack of evidence that directly compared the two treatments. There were uncertainties around the comparability of the patient populations in the clinical trials, which the Assessment Group considered undermined the robustness of the indirect comparison. In addition, there were limitations in developing a robust economic analysis for this comparison, as key data required for the model for CAV were missing (including survival curves for time to progression and utility data). However, the Assessment Group provided a detailed cost comparison of oral topotecan compared with CAV and also a threshold analysis showing what magnitude of QALY gain and

respective utility difference would need to be achieved with oral topotecan to make it a cost-effective alternative to CAV.

4.2.18 The total chemotherapy cost per cycle calculated by the Assessment Group for CAV was £740.29 (first cycle) and £669.41 (subsequent cycles) and for oral topotecan was £911.64, resulting in a higher cost for oral topotecan of between £171 and £242 per cycle. Total costs of chemotherapy were calculated to be between £900 and £1800 higher for oral topotecan compared with CAV, depending on the number of cycles of CAV provided (3 or 4 cycles) and whether costs of managing adverse events were included.

4.2.19 In the Assessment Group's threshold analysis, it was calculated that QALY gains of between 0.03 and 0.09 were required for oral topotecan to be cost effective compared with CAV depending on:

- the number of cycles of CAV received (3 or 4 cycles)
- whether adverse event costs were included
- the cost-effectiveness threshold assumed.

As the evidence suggested no survival benefit for oral topotecan compared with CAV, any QALY gains would need to arise from quality-of-life improvements or higher utilities for patients who received oral topotecan. A number of different scenarios were developed based on possible time intervals over which oral topotecan might produce a higher utility than CAV. These included receiving oral rather than intravenous chemotherapy (9 weeks or 12 weeks of utility gain), differences in symptom improvements (20 weeks or 28 weeks of utility gain), and increased time to worsening of symptoms (9.4 weeks of utility gain). Utility differences of between 0.06 and 0.52 would be required to achieve the minimum QALY gains for oral topotecan to be cost effective compared with CAV depending on:

- the number of cycles of CAV received (3 or 4 cycles)

- whether adverse event costs were included
- the cost-effectiveness threshold assumed
- the duration of the utility gain with oral topotecan.

4.3 Consideration of the evidence

4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of topotecan for the treatment of relapsed small-cell lung cancer, having considered evidence on the nature of small-cell lung cancer and the value placed on the benefits of topotecan for the treatment of relapsed small-cell lung cancer by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.3.2 The Committee reviewed the clinical-effectiveness results for the trials included in the review by the Assessment Group. The Committee noted the statistically significant improvement in overall survival for oral topotecan plus best supportive care compared with best supportive care alone. It also noted that the mean change in the EQ-5D score from baseline for the pooled analysis and the last evaluation analysis (section 4.1.3) showed a statistically significant difference for oral topotecan plus best supportive care compared with best supportive care alone, indicating a smaller decline in health status for those patients receiving oral topotecan plus best supportive care. The Committee noted that the reasons for further intravenous chemotherapy being considered unsuitable for the patients in the study were not reported by the investigators. However, the Committee concluded that this study confirmed the clinical effectiveness of oral topotecan in extending survival relative to best supportive care alone in people with relapsed small-cell lung cancer.

4.3.3 The Committee discussed the results of the two clinical trials that compared oral topotecan with intravenous topotecan. It noted that

there were no statistically significant differences between oral topotecan and intravenous topotecan in any of the clinical outcomes measured in either of the trials. The Committee accepted that oral topotecan and intravenous topotecan were similar in terms of clinical efficacy. The Committee was aware that adverse events were similar between intravenous topotecan and oral topotecan, with the exception of neutropenia, which appeared to occur more frequently with intravenous topotecan. The Committee heard from the clinical specialist and patient expert that intravenous treatment with topotecan required patients to attend hospital for 5 consecutive days each cycle which was inconvenient for patients and costly. The Committee concluded that intravenous topotecan had no clinical advantages over oral topotecan.

- 4.3.4 The Committee then discussed the trial that compared intravenous topotecan with CAV. It noted that patients receiving intravenous topotecan showed a higher overall response rate compared with CAV, but that this was not statistically significant. The results for overall survival, median response duration, median time to response and median time to progression were also not statistically significantly different. The Committee noted that a greater proportion of patients who received intravenous topotecan reported improvements in symptoms of dyspnoea, anorexia, hoarseness, fatigue and interference with daily activity, and that these differences were statistically significant. However, it was aware that symptoms were measured using an unvalidated instrument. The Committee heard from the clinical specialist that these symptoms were likely to be related to disease activity, and would be expected to be similar if the response rates were the same. The Committee concluded that intravenous topotecan might have some benefits over CAV in terms of symptomatic relief, but these were difficult to confirm or quantify on the basis of current evidence. The Committee also noted that CAV only required patients to attend

hospital once per cycle compared with five times for intravenous topotecan. The Committee concluded that the effectiveness of the two regimens was similar, that some symptomatic gains were conceivable with intravenous topotecan, but that CAV was more convenient for patients because of the lower requirement for hospital attendance.

4.3.5 The Committee considered the clinical trial that compared intravenous topotecan with intravenous amrubicin. The Committee noted that the trial used a lower dose of topotecan than is currently licensed and used in the UK. It also noted that amrubicin does not currently hold a marketing authorisation for use in the UK. It heard from the clinical specialist that amrubicin is not routinely used in UK clinical practice and there are limited data available on the clinical effectiveness of amrubicin for small-cell lung cancer. It therefore concluded that amrubicin should not be considered as a comparator for topotecan.

4.3.6 The Committee then reviewed the economic analyses presented by the manufacturer and the Assessment Group. The Committee noted that the manufacturer's model gave an ICER for oral topotecan plus best supportive care compared with best supportive care alone of £26,800 per QALY gained in patients for whom intravenous chemotherapy was considered unsuitable, compared with the Assessment Group model which gave an ICER of £33,900 per QALY gained. It was aware that the difference in the results was mainly driven by the different methods used to manage missing utility data. The manufacturer used the mean utility score (across both trial arms) for missing values up to cycle 12 and the last observation carried forward after that, whereas the Assessment Group used regression analysis to calculate a daily reduction in utility from the study data and applied this to the baseline utility value. The Committee preferred the method adopted by the Assessment Group, because it considered that a declining utility

over time was a more accurate reflection of what happened in real life for this population than a constant utility value.

4.3.7 The Committee understood that the manufacturer had argued that the Assessment Group's model undercounted disease monitoring costs in the control arm. The Committee heard that this would only be an issue if monitoring was as intensive off treatment as on treatment, but the clinical specialist confirmed that this is not current UK practice. Thus the Committee concluded that the Assessment Group's approach to monitoring costs was acceptable.

4.3.8 Overall, the Committee considered the Assessment Group's model to be preferred even though it was based on aggregated data rather than individual patient data. Furthermore, taking into account the sensitivity analyses presented by the Assessment Group, the Committee concluded that the ICER for oral topotecan compared with best supportive care was unlikely to be much greater than that resulting from the Assessment Group base-case analysis. The Committee noted that the Assessment Group's analysis showed that the ICER for intravenous topotecan versus oral topotecan was either very high or that intravenous topotecan was dominated. It also noted that the ICER for intravenous topotecan compared with best supportive care was very high. The Committee therefore concluded that intravenous topotecan could not be recommended for the treatment of relapsed small-cell lung cancer.

4.3.9 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy, and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed, or otherwise indicated, for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case economic modelling are plausible, objective and robust.

4.3.10 With respect to the comparison between oral topotecan and best supportive care for people in whom treatment with CAV is contraindicated and who would otherwise receive only best supportive care, the Committee considered whether the evidence for this group satisfied the criteria for end-of-life treatments. The Committee noted from the clinical trial that normal life expectancy with best supportive care alone was unlikely to be greater than 24 months and was potentially as low as 14 weeks. It also noted that oral topotecan extended survival by approximately 12 weeks in the clinical trial and 17 weeks in the Assessment Group's model. The Committee noted that median overall survival of 25.9 weeks for patients receiving oral topotecan compared with 13.9 weeks receiving best supportive care alone had been seen in a clinical trial. The Committee concluded that the evidence in support of extended survival with oral topotecan was sufficiently robust. The Committee was aware that the number of patients with relapsed small-cell lung cancer in England and Wales was between 800 and 1600. Although the Committee noted that topotecan is licensed for other indications than for which it is being appraised, the Committee considered topotecan to fulfil the small population criterion for an end-of-life treatment. The Committee agreed that

the evidence for oral topotecan for people in whom treatment with CAV is contraindicated and who would otherwise receive only best supportive care satisfied the criteria for end-of-life treatments.

4.3.11 The Committee next considered the cost-effectiveness estimate for oral topotecan calculated by the Assessment Group, in light of the appraisal of a life-extending, end-of-life treatment. It considered the impact of giving a greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy person of the same age and the magnitude of additional weight that would need to be assigned to the original QALY benefits in this patient group for the cost effectiveness of the drug to fall within the current threshold range. Although the best estimate of the ICER for oral topotecan plus best supportive care compared with best supportive care alone was in excess of the normal range for cost effectiveness for the NHS, the Committee concluded that oral topotecan should be recommended for patients with relapsed small-cell lung cancer for whom re-treatment with the first-line regimen is not considered appropriate, and for whom treatment with CAV is contraindicated. (For details of the contraindications to CAV see the summary of product characteristics for each of the component drugs).

4.3.12 The Committee then considered the role of oral topotecan for patients who were able to receive CAV. The Committee heard from the clinical specialist that most patients who were well enough to receive chemotherapy of any kind would be able to receive CAV. The Committee considered that although there were no clinical data available that directly compared oral topotecan with CAV, it was reasonable to assume equivalence in effectiveness from the trial comparing intravenous topotecan with CAV. The clinical specialist and the patient expert stated that even when CAV was appropriate, some patients might prefer treatment with oral

topotecan because it is more convenient to take treatment at home rather than attending hospital for intravenous treatment. However, the Committee noted that no consultees or commentators suggested that oral topotecan had a place when CAV was appropriate. Furthermore the Committee noted that neither the manufacturer nor the Assessment Group provided a detailed economic analysis comparing oral topotecan with CAV. It discussed the detailed cost comparison provided by the Assessment Group and noted the higher total treatment costs associated with oral topotecan compared with CAV. The Committee also considered the threshold analysis that calculated the minimum QALY gains required for oral topotecan to be cost effective compared with CAV, and the associated utility gains needed to achieve the minimum QALY gain. The Committee agreed that it was unlikely that the actual utility differences between the two treatments would be large enough to achieve the minimum QALY gains required for oral topotecan to be cost effective compared with CAV. The Committee therefore concluded that it could not recommend oral topotecan as an alternative treatment to CAV for the treatment of relapsed small-cell lung cancer.

5 Implementation

- 5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. The NHS is not required to fund treatments that are not recommended by NICE.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing report and costing template to estimate the savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives which support this locally.
- Audit support for monitoring local practice.

6 Ongoing research

6.1 The Committee noted the following ongoing clinical trials related to this appraisal.

- NCT00547651 is a phase III, randomised controlled trial comparing intravenous amrubicin (40 mg/m²) with intravenous topotecan (1.5 mg/m²) in adults with extensive-stage or limited-stage small-cell lung cancer sensitive or refractory to first-line (platinum-based) chemotherapy. Estimated study completion date: March 2011.

7 Related NICE guidance

Published

- Lung cancer: the diagnosis and treatment of lung cancer. NICE clinical guideline 24 (2005). Available from www.nice.org.uk/CG24

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Lung cancer – update: the diagnosis and treatment of lung cancer (update of NICE clinical guideline 24). NICE clinical guideline (publication expected March 2011).

8 Review of guidance

- 8.1 The guidance on this technology will be considered for review by the Guidance Executive in November 2012.

Andrew Stevens
Chair, Appraisal Committee
September 2009

Appendix A: Appraisal Committee members, guideline representatives and NICE project team

A Appraisal Committee members

The Appraisal Committee is one of NICE's standing advisory committees. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice chair. Each branch considers its own list of technologies, and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Kathryn Abel

Reader and Consultant Psychiatrist, University of Manchester

Professor David Barnett

Professor of Clinical Pharmacology, University of Leicester

Dr David W Black

Director of Public Health, Derbyshire County Primary Care Trust

Dr Brian Buckley

Lay Member

Mark Campbell

Director of Standards and Performance, Bury PCT

Professor Mike Campbell

Professor of Medical Statistics, University of Sheffield

Mr David Chandler

Lay Member

Dr Peter Clark

Consultant Medical Oncologist, Clatterbridge Centre for Oncology

Dr Christine Davey

Senior Researcher, North Yorkshire Alliance R&D Unit

Dr Mike Davies

Consultant Physician, Royal Infirmary, Manchester

Mr Richard Devereaux-Philips

Public Affairs Manager, Medtronic Ltd

Professor Rachel Elliot

Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Peter Jackson

Clinical Pharmacologist, University of Sheffield

Professor Peter Jones

Pro Vice Chancellor for Research & Enterprise, Keele University

Professor of Statistics, Keele University

Mr Henry Marsh

Consultant Neurosurgeon, St George's Hospital London

Professor Jonathan Michaels (Vice Chair)

Professor of Vascular Surgery, University of Sheffield

Dr Eugene Milne

Deputy Medical Director, North East Strategic Health Authority

Professor Simon Mitchell

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Dr Richard Alexander Nakielny

Consultant Radiologist, Royal Hallamshire Hospital, Sheffield

Mrs Ruth Oliver-Williams

Head of Nursing, Quality Improvement Lead Surgical Services, Royal Derby Hospital, Derby

Dr Katherine Payne

Health Economics Research Fellow, University of Manchester

Dr Danielle Preedy

Lay Member

Dr Philip Rutledge

General Practitioner, Consultant in Medicines Management, NHS Lothian

Dr Surinder Sethi

Consultant in Public Health Medicine, North West Specialised Services Commissioning Team

Professor Andrew Stevens (Chair)

Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

Dr Matt Stevenson

Technical Director, School of Health and Related Research Technical Assessment Group, University of Sheffield

Dr Cathryn Thomas

Associate Professor and General Practitioner, University of Birmingham

B Guideline representatives

The following individuals, representing the Guideline Development Group responsible for developing NICE's clinical guideline related to this topic, were invited to attend the meeting to observe and to contribute as advisers to the Committee.

- Dr Jeremy Braybrooke, Consultant Medical Oncologist, British Haematology and Oncology Centre University Hospitals Bristol NHS Foundation Trust – representing National Collaborating Centre for Cancer

C NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Helen Knight

Technical Lead

Janet Robertson

Technical Adviser

Laura Malone

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by Southampton Health Technology Assessments Centre, University of Southampton:

- Loveman E, Jones J, Hartwell D et al. The clinical and cost effectiveness of topotecan for small cell lung cancer: a systematic review and economic evaluation, March 2009

B Additional evidence for this appraisal was prepared by Southampton Health Technology Assessments Centre, University of Southampton:

- Loveman E, Jones J, Hartwell D et al. Addendum to SHTAC's Technology Assessment Report on the clinical and cost effectiveness of topotecan for small cell lung cancer: a systematic review and economic evaluation, August 2009

C The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- GlaxoSmithKline (oral and intravenous topotecan)

II Professional/specialist and patient/carer groups:

- British Thoracic Society
- Royal College of Nursing
- Royal College of Physicians (Medical Oncology Joint Special Committee)
- Breathe Easy
- Macmillan Cancer Support
- Roy Castle Lung Cancer Foundation
- South Asian Health Foundation

III Other consultees

- Department of Health
- Berkshire East Teaching PCT
- Powys LHB PCT
- Welsh Assembly Government

IV Commentator organisations (did not provide written evidence and without the right of appeal)

- Department of Health, Social Services and Public Safety for Northern Ireland
- NHS Quality Improvement Scotland
- Pfizer (cyclophosphamide, doxorubicin)
- Southampton Health Technology Assessments Centre, University of Southampton
- National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme)
- National Collaborating Centre for Cancer

D The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on topotecan for the treatment of relapsed small-cell lung cancer by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Jesme Fox, Medical Director of The Roy Castle Lung Cancer Foundation, nominated by The Roy Castle Lung Cancer Foundation – patient expert
- Dr Jeremy Braybrooke, Consultant Medical Oncologist, British Haematology and Oncology Centre University Hospitals Bristol NHS Foundation Trust, representing National Collaborating Centre for Cancer – clinical specialist