NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Topotecan for the treatment of recurrent and stage IVB cervical cancer

This guidance was developed using the single technology appraisal (STA) process

1 Guidance

1.1 Topotecan in combination with cisplatin is recommended as a treatment option for women with recurrent or stage IVB cervical cancer only if they have not previously received cisplatin.

1.2 Women who have previously received cisplatin and are currently being treated with topotecan in combination with cisplatin for recurrent and stage IVB cervical cancer should have the option to continue their therapy until they and their clinicians consider it appropriate to stop.

2 The technology

2.1 Topotecan (Hycamtin, GlaxoSmithKline) prevents DNA replication in cancer cells by inhibiting the enzyme topoisomerase I. Topotecan in combination with cisplatin has a marketing authorisation for patients with carcinoma of the cervix recurrent after radiotherapy and for patients with stage IVB disease. The summary of product characteristics (SPC) states that patients with prior exposure to cisplatin require a sustained treatment-free

interval to justify treatment with topotecan in combination with cisplatin.

2.2 The recommended dosage is 0.75 mg/m^2/day topotecan, administered as a 30-minute intravenous infusion on days 1, 2 and 3 of each cycle. Cisplatin is administered after topotecan as an intravenous infusion on day 1 at a dosage of 50 mg/m^2/day. Treatment should be repeated every 21 days for six cycles or until disease progresses. Topotecan should only be readministered if the neutrophil count is at least 1.5 x 10^9 per litre, the platelet count is at least 100 x 10^9 per litre, and the haemoglobin level is at least 9 g/100 ml (after transfusion if necessary). The SPC states that topotecan should only be used in units specialised in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a physician experienced in the use of chemotherapy.

2.3 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. Cisplatin causes nausea and vomiting in the majority of patients. Serious toxic effects of cisplatin on the kidneys, bone marrow and hearing function are common. Serum electrolyte disturbances, hyperuricaemia, allergic reactions and cardiovascular abnormalities have also been reported. For full details of adverse effects and contraindications, see the SPC.

2.4 The acquisition cost of topotecan is £97.65 for a 1-mg vial or £290.62 for a 4-mg vial (excluding VAT; 'British national formulary' [BNF] edition 57). The acquisition cost of cisplatin is £24.50 for a 50-mg vial or £50.22 for a 100-mg vial (excluding VAT; BNF edition 57). Assuming a body surface area of 1.7 m^2, the total dose per cycle would be 3.825 mg topotecan (that is, 1.275 mg/day).

Assuming excess topotecan is wasted after each dose, a total of six 1-mg vials would be required at a cost of £585.90. For cisplatin, the cost for the required 85 mg would be £49 for two 50-mg vials. The cost of topotecan for a full course of six cycles is £3515.40. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of topotecan and a review of this submission by the Evidence Review Group (ERG; appendix B).

3.1 In the submission, the manufacturer compared topotecan plus cisplatin with cisplatin alone. The manufacturer also compared topotecan plus cisplatin with paclitaxel plus cisplatin. The manufacturer justified their choice of comparator with data from the IMS Oncology Analyzer database from 2004 to 2008 to show that cisplatin alone is the most frequently used therapy in the group of women for whom topotecan plus cisplatin is licensed (39%). A more recent breakdown of the IMS Oncology Analyzer database from 2006 to 2008 indicates that 27% of patients receive cisplatin alone; 23% receive carboplatin plus paclitaxel. There are a range of other combination therapies, each of which is given to fewer than 10% of patients. In total 57% of patients receive some form of combination therapy.

3.2 The manufacturer identified one phase III, open-label randomised controlled trial (GOG-0179; n = 293) that included women with persistent, recurrent or stage IVB cervical cancer and compared topotecan plus cisplatin with cisplatin alone. These women were followed up for a maximum of 36 months. The trial reported increased median overall survival for topotecan plus cisplatin

compared with cisplatin alone: 9.4 versus 6.5 months, respectively (hazard ratio [HR] 0.76; 95% confidence interval [CI] 0.59 to 0.98; p = 0.033), and increased median progression-free survival for topotecan plus cisplatin compared with cisplatin alone: 4.6 versus 2.9 months, respectively (HR 0.76; 95% CI 0.60 to 0.97; p = 0.027).

3.3 The manufacturer reported that the safety profile for topotecan plus cisplatin was predictable and manageable. However, there were four treatment-related deaths in the topotecan plus cisplatin group compared with none in the cisplatin group. Febrile neutropenia occurred in 17.7% of women treated with topotecan plus cisplatin and in 7.5% of women treated with cisplatin alone. Serious adverse events occurred in 10% of women treated with cisplatin alone compared with 14% of women treated with topotecan plus cisplatin.

3.4 The manufacturer presented data on subpopulations of the GOG-0179 trial. The 'licensed population', which consisted of 222 women, was defined as the population for whom topotecan is indicated in the marketing authorisation. Data from the other 71 women in the trial were excluded because they had cervical cancer that was not covered by the marketing authorisation (32 women had persistent disease and in 39 women the sustained cisplatin-free interval was less than 180 days). The median overall survival estimates for the licensed population were 11.9 months for topotecan plus cisplatin (n = 107) and 7.3 months for cisplatin alone (n = 115) (HR 0.65; 95% CI 0.49 to 0.88; p = 0.0041).

3.5 The manufacturer completed further subgroup analyses of the licensed population to consider the benefits of topotecan in women who had never had cisplatin (cisplatin naive; n = 120) and those with a sustained cisplatin-free interval longer than 180 days (n = 102). The median overall survival in the cisplatin-naive group was 14.5 months for topotecan plus cisplatin and 8.5 months for

cisplatin alone (HR 0.59; 95% CI 0.39 to 0.88; p = 0.0098). The median overall survival in the sustained cisplatin-free interval group was 9.9 months for topotecan plus cisplatin and 6.3 months for cisplatin alone (HR 0.75; 95% CI 0.49 to 1.16; p = 0.1912).

3.6 The manufacturer identified a trial (GOG-0204) that was not formally included in the clinical-effectiveness review. An abstract reported on this trial, which included a head-to-head comparison of four cisplatin-containing combinations: paclitaxel (n = 103), vinorelbine (n = 108), gemcitabine (n = 112) and topotecan (n = 111). A planned interim analysis recommended early closure of GOG-0204 because the comparator groups were unlikely to demonstrate a statistically significant benefit compared with paclitaxel plus cisplatin. For the comparison of cisplatin plus topotecan with cisplatin plus paclitaxel, the trial reported a hazard ratio for progression-free survival of 1.268 and for overall survival of 1.255. The differences favoured the paclitaxel combination but were not statistically significant.

3.7 The manufacturer identified another trial (GOG-0169) which was used in an indirect comparison of topotecan plus cisplatin and paclitaxel plus cisplatin. This phase III study compared paclitaxel plus cisplatin (n = 130) with cisplatin alone (n = 134) in women with stage IVB, recurrent, or persistent squamous cell cervical cancer. The trial duration was 24 months. The median overall survival was 9.7 months for paclitaxel plus cisplatin and 8.8 months for cisplatin alone. The median progression-free survival was 4.8 months for paclitaxel plus cisplatin and 2.8 months for cisplatin alone.

3.8 The manufacturer submitted two separate cost-effectiveness analyses:

- A within-trial comparison between topotecan plus cisplatin and cisplatin alone using a time horizon of 36 months and patient-level data from the GOG-0179 trial.
- A model-based comparison of topotecan plus cisplatin and paclitaxel plus cisplatin, using a time horizon of 24 months and data from the GOG-0179 and GOG-0169 trials.

In the submission the results of the within-trial comparison were reported as cost per quality-adjusted life year (QALY) gained and in the model-based comparison as cost per life year gained. In response to a request from the ERG, an additional model-based comparison was presented expressing outcomes in terms of both life years gained and QALYs gained.

3.9 For the within-trial comparison the manufacturer performed separate analyses for the licensed population and subgroups of this population. The subgroups were women who were cisplatin naive and women who had had a sustained cisplatin-free period. The manufacturer stated that the least potentially biased analysis in the model-based comparison would be between the cisplatin-naive population of GOG-0179, including women with persistent disease, and the overall intention-to-treat population of GOG-0169. The manufacturer considered the within-trial comparison to be the primary analysis within their submission. The model-based comparison was presented as a secondary analysis to include alternative comparators used in England and Wales.

3.10 In the within-trial comparison, the manufacturer included patient-level data for clinical efficacy, safety and quality of life from the GOG-0179 trial. Data on resource use were based on clinical events occurring in the trial supplemented by data from external sources, including expert opinion. Costs were obtained from published sources, including NHS Reference Costs 2006/07. The

manufacturer did not give a breakdown of the costs for the within-trial comparison. It was assumed that the cost of topotecan was £488.25 per cycle and the cost of cisplatin was £50.74 per cycle. The cost of topotecan was varied in a sensitivity analysis from £390.60 to £585.90 to reflect minimum wastage of unused topotecan (when vials were reused over the 3-day dosing schedule) and maximum wastage (when vials were discarded immediately after use). The cost of administering topotecan was assumed to be £277 for the first dose of each cycle and £51 for each subsequent dose in each cycle.

3.11 The manufacturer incorporated quality-of-life benefits into the within-trial comparison using an algorithm linking a disease-specific measure of quality of life (Functional Assessment of Cancer Therapy – General [FACT-G]) to utility. Utility values differed depending on whether a woman was treated with cisplatin alone or topotecan plus cisplatin. Values also differed according to the treatment phase: prior to randomisation, prior to cycle 2, prior to cycle 5 and 9 months after randomisation. The values for the cisplatin-alone group were 0.79, 0.73, 0.58 and 0.33, for these four treatment phases respectively. The corresponding values for the topotecan plus cisplatin group were 0.79, 0.72, 0.66 and 0.45. The manufacturer also included a review of the literature of alternative utility data associated with cervical cancer and other gynaecological cancers (including breast cancer). The utility values used in the sensitivity analysis were identified from a study of breast cancer (Brown and Hutton 1998) and were 0.64 at the start of treatment, 0.81 to reflect response to treatment, 0.39 following progression of disease and 0.16 during the last week of life.

3.12 In the model-based comparison the manufacturer based the key analysis on aggregate data from indirectly comparing the GOG-0179 and GOG-0169 trials. GOG-0169 did not report the hazard

ratio for overall survival, therefore the manufacturer estimated the hazard ratio from the survival curves (HR = 0.87; 95% CI 0.68 to 1.11). The estimated hazard ratio was then applied to the observed overall survival for the cisplatin group of GOG-0179 to estimate the overall survival for paclitaxel plus cisplatin in the model-based comparison. The hazard ratio for the compared trials was 0.72 (95% CI 0.46 to 1.15). An additional sensitivity analysis included direct data on this comparison from the GOG-0204 trial. Resource use in the model-based comparison was based on the costing algorithms developed for the within-trial comparison. The utility values from the literature review were included in the cost per QALY analyses.

3.13 In the within-trial comparison, the base-case results for the licensed population were an incremental QALY gain of 0.23 at an incremental cost of £4122, giving an incremental cost-effectiveness ratio (ICER) of £17,974 per QALY gained. Probabilistic sensitivity analysis suggested that the probability of topotecan being cost effective at £20,000 and £30,000 per QALY gained was 50% and 88% respectively. For the cisplatin-naive population (including women with stage IVB cervical cancer) the incremental QALY gain was 0.32 at an incremental cost of £3521, giving an ICER of £10,928 per QALY gained. Probabilistic sensitivity analysis suggested that the probability of topotecan being cost effective at £20,000 and £30,000 per QALY gained was 89% and 98% respectively. For the sustained cisplatin-free interval population the incremental QALY gain was 0.13 at an incremental cost of £4145, giving an ICER of £32,463 per QALY gained. Probabilistic sensitivity analysis suggested that the probability of topotecan being cost effective at £20,000 and £30,000 per QALY gained was 31% and 55% respectively.

3.14 In the model-based comparison, the manufacturer only presented results for the cisplatin-naive population (including women with persistent disease). In the base-case results topotecan plus cisplatin dominated paclitaxel plus cisplatin (that is, paclitaxel plus cisplatin was less effective and more expensive), and had an ICER of £19,964 per life year gained compared with cisplatin alone. Using the hazard ratio from GOG-0204 (rather than from GOG-0169), paclitaxel plus cisplatin had an ICER of £982 per life year gained compared with topotecan plus cisplatin. In response to a request for clarification from the ERG, the manufacturer submitted a revised model-based comparison incorporating health-related quality of life and a time horizon of 36 months. When the hazard ratio from GOG-0169 was used, topotecan plus cisplatin dominated paclitaxel plus cisplatin; when the hazard ratio from GOG-0204 was used, paclitaxel plus cisplatin had an ICER of £13,260 per QALY gained compared with topotecan plus cisplatin.

3.15 The ERG identified a number of differences between the inclusion criteria of the clinical trials. GOG-0179 included women who were previously untreated, or had received prior chemotherapy or radiotherapy with or without a radiosensitiser. Approximately 60% of women had received prior cisplatin either as chemotherapy or as a radiosensitiser. GOG-0169 excluded women who had received prior chemotherapy, but included women who had been given chemotherapy as part of radiosensitisation (approximately 30%). However, it was unclear how many women received cisplatin as a radiosensitiser. GOG-0204 also excluded women who had previously received chemotherapy, unless this was given as a radiosensitiser, and the proportion of women who had previously received cisplatin as a radiosensitiser was approximately 70%. The ERG considered that GOG-0204 may be more representative of the UK population than GOG-0169, because of the increasing

number of women in the UK who receive cisplatin as first-line treatment or as a radiosensitiser. The ERG stated that the manufacturer had included treatments currently used in the UK, but had not explained why other potentially relevant comparators were not included such as cisplatin plus 5-fluorouracil and cisplatin plus mitoxantrone.

3.16 The ERG stated that it was unclear from the manufacturer's submission whether a complete network of evidence had been identified and investigated. GOG-0179 was a well-conducted randomised controlled trial and it was reasonable for the manufacturer to use this as the direct comparison. However, head-to-head comparisons were also available from GOG-0204. The ERG considered such a direct comparison of topotecan plus cisplatin and paclitaxel plus cisplatin would have been preferable to the indirect comparison used, particularly given the differences in populations between GOG-0169 and GOG-0179. The inclusion of GOG-0204 would also have increased the number of potential comparators and expanded the network of indirect evidence.

3.17 The ERG stated that a complete validation of the within-trial comparison was not possible because complete data sets and coding had not been provided within the timelines of the ERG critique. In addition, the ERG raised concerns about the external validity of this comparison. When comparing the two economic analyses, the ERG noted a difference in the mean costs obtained from the within-trial comparison and the model-based comparison. The ERG was unable to fully investigate the difference because a breakdown of the costs was not provided for the within-trial comparison. The ERG noted that the utility estimates did not appear to have been derived accurately from the trial because of incorrect mapping of FACT-G data to utility values. In addition, there were concerns about the imputation methods and that the

impact of mortality may have been double counted. Furthermore, the ERG questioned the appropriateness of the utility values used in the model-based comparison and sensitivity analysis because they were from a study on metastatic breast cancer and not cervical cancer. The ERG raised concerns about the costing in both analyses, particularly costs relating to administration and adverse events.

3.18 The ERG undertook a number of exploratory analyses for both the cisplatin-naive and the licensed populations using the model-based comparison. The ERG amended the utility values, the costs of administering topotecan and the assumed number of vials of topotecan used per treatment cycle. The ERG also performed exploratory analyses that considered dose reduction.

3.19 To address the limitations in the utility values available, the ERG considered three scenarios. The first used the manufacturer's starting utility value (Brown and Hutton 1998; 0.64) adopted for the model-based comparison. The second used a slightly higher starting utility value of 0.67 taken from literature estimates of mean utility values associated with cervical cancer, weighted according to the proportion of patients with each stage of disease in GOG-0179. Values for subsequent health states were calculated using the Brown and Hutton 1998 utility values. This second scenario assumed that utility remained constant from starting treatment to disease progression. The third scenario was the same as the second but used a starting utility value of 0.72 derived from the FACT-G data collected in GOG-0179. The ICERs for topotecan plus cisplatin compared with cisplatin alone for the cisplatin-naive population for the three utility scenarios were £25,309, £26,156 and £24,513 per QALY gained respectively. The ICERs for the licensed population for the three utility scenarios were £55,926, £59,406 and £54,352 per QALY gained respectively. The ERG used the third

scenario in all subsequent exploratory analyses because they considered it the most appropriate.

3.20 The ERG considered that the costs of administering topotecan may have been underestimated. The ERG stated that more appropriate estimates of the administration costs for each treatment could be taken from the health resource group code SB14Z for the delivery of complex chemotherapy, including prolonged infusion treatment at first attendance, and code SB15Z for the delivery of subsequent elements of a chemotherapy cycle, given in NHS Reference Costs 2006/07. The cost code SB14Z (£289, inflated to £299 at 2007/08 prices) was assumed to reflect the administration of cisplatin, paclitaxel plus cisplatin, or the first administration of topotecan plus cisplatin. The cost code SB15Z (£189, inflated to £195 at 2007/08 prices) was assumed to reflect the second and third administration of topotecan for each cycle. The total cost of administering topotecan plus cisplatin was £689 per cycle, while the cost of administering cisplatin alone or paclitaxel plus cisplatin was £299 per cycle. The ICER for topotecan plus cisplatin compared with cisplatin alone (including the amended utilities) was £31,831 per QALY gained in the cisplatin-naive population and £68,885 per QALY gained in the licensed population. The revised administration costs were used in subsequent exploratory analyses.

3.21 The ERG had concerns about the number of topotecan vials used and the amount of wastage in the manufacturer's analysis. In the cisplatin-naive population the ICERs for topotecan plus cisplatin compared with cisplatin alone (including the amended utilities and administration costs) were £26,778 and £34,327 per QALY gained, for minimum and maximum wastage respectively. For the licensed population the ICERs were £58,872 and £73,833 per QALY gained respectively.

3.22 The ERG considered that the differences in costs between the within-trial comparison and the model-based comparison may have been because of dose reduction. The ERG therefore calculated the difference in costs between the manufacturer's model-based comparison and the ERG's revised cost estimates. The differences were then applied to the absolute estimates of costs in the within-trial analysis. Both minimum and maximum wastage of vials were considered. When wastage was minimised, the ICER for topotecan plus cisplatin compared with cisplatin alone was £19,815 per QALY gained in the cisplatin-naive population and £53,868 per QALY gained in the licensed population. When maximum wastage of topotecan was assumed, the ICERs were £27,362 and £68,826 per QALY gained respectively.

3.23 The manufacturer's model-based comparison did not report an ICER for any treatment in comparison with cisplatin alone. The ERG integrated the cost and QALY values for cisplatin into the manufacturer's model-based comparison so that cisplatin could be considered as a comparator alongside topotecan plus cisplatin and paclitaxel plus cisplatin. This allowed for a simultaneous incremental analysis to be carried out between the three treatments. The ERG presented two separate scenarios, one using the hazard ratio from the indirect comparison of GOG-0169 and GOG-0179 and another using the hazard ratio from GOG-0204. Both included the amended utility values and administration costs, but neither included dose reduction. When the hazard ratio from the indirect comparison of GOG-0169 and GOG-0179 was used and minimum wastage assumed, the ICER was £26,778 per QALY gained for topotecan plus cisplatin compared with cisplatin alone in the cisplatin-naive population and £58,872 per QALY gained in the licensed population. When maximum wastage was assumed, the ICER was £34,327 per QALY gained for topotecan plus cisplatin

compared with cisplatin alone for the cisplatin-naive population. In this scenario paclitaxel plus cisplatin was extendedly dominated (that is, the ICER was higher than that of the next, more effective, alternative). For the licensed population the ICER for topotecan plus cisplatin compared with paclitaxel plus cisplatin was £116,788 per QALY gained, and the ICER for paclitaxel plus cisplatin in comparison with cisplatin alone was £64,865 per QALY gained. When the GOG-0204 hazard ratio was used, topotecan plus cisplatin was dominated by paclitaxel plus cisplatin regardless of the assumption about topotecan wastage (that is topotecan plus cisplatin was more expensive and less effective than paclitaxel plus cisplatin). The ICER for paclitaxel plus cisplatin compared with cisplatin alone was £17,021 per QALY gained for the cisplatin-naive population and £21,926 per QALY gained for the licensed population.

3.24 Following consultation on the appraisal consultation document, the manufacturer of topotecan provided a network meta-analysis of clinical-effectiveness data and further economic analyses. The network meta-analysis pooled estimates of effectiveness derived from direct and indirect comparisons of the three relevant clinical trials for cisplatin, paclitaxel plus cisplatin and topotecan plus cisplatin: GOG-0179, GOG-0169 and GOG-0204. The overall survival hazard ratios for the comparison of cisplatin plus paclitaxel with cisplatin alone were 0.83 (95% CI 0.68 to 1.08) for the cisplatin-naive population and 0.81 (95% CI 0.67 to 1.03) for the licensed population, favouring the paclitaxel combination. The corresponding hazard ratios for the comparison of cisplatin plus topotecan with cisplatin alone were 0.75 (95% CI 0.53 to 0.97) and 0.81 (95% CI 0.62 to 0.98), favouring the topotecan combination. For the comparison of cisplatin plus topotecan with cisplatin plus paclitaxel the hazard ratio for the cisplatin-naive population was

0.98 (95% CI 0.73 to 1.23). A hazard ratio was not presented for the licensed population.

3.25 The manufacturer included the hazard ratios obtained from the network meta-analysis in a revised economic analysis. A further economic analysis was also presented that used the hazard ratio for topotecan from GOG-0179, but data from the meta-analysis for the cisplatin survival curves. In addition, the economic model was updated to provide fully incremental analyses (that is, to provide a simultaneous comparison of all three treatment options) and to include a probabilistic function, to capture the uncertainty of the results. Revised parameter assumptions were also incorporated to include the ERG's preferred utility values, preferred administration costs and assumptions of maximum and minimum wastage. Results were presented for both the licensed population and the cisplatin-naive population.

3.26 For the licensed population, using the hazard ratios from the meta-analysis and assuming maximum wastage, the ICER for topotecan plus cisplatin was £81,756 per QALY gained in comparison with cisplatin alone and was dominated by paclitaxel plus cisplatin. If minimum wastage of topotecan was assumed, the ICER for topotecan plus cisplatin was £63,913 per QALY gained in comparison with cisplatin alone and was dominated by paclitaxel plus cisplatin.

3.27 For the licensed population, using the hazard ratios from GOG-0179 for topotecan survival and hazard ratios from the meta-analysis for the cisplatin survival curves, and assuming maximum wastage, the ICER for topotecan plus cisplatin was £60,903 per QALY gained in comparison with cisplatin alone and £65,364 per QALY gained in comparison with paclitaxel plus cisplatin. If minimum wastage of topotecan was assumed, the ICER was

£47,616 per QALY gained in comparison with cisplatin alone, and £7142 per QALY gained in comparison with paclitaxel plus cisplatin.

3.28 For the cisplatin-naive subgroup, using the hazard ratios from the meta-analysis and assuming maximum wastage of topotecan, the ICER for topotecan plus cisplatin was £58,911 per QALY gained in comparison with cisplatin alone, and £49,964 in comparison with paclitaxel plus cisplatin. If minimum wastage of topotecan was assumed, the ICER for topotecan plus cisplatin was £46,054 per QALY gained in comparison with cisplatin alone and £5459 per QALY gained in comparison with paclitaxel plus cisplatin.

3.29 For the cisplatin-naive subgroup, using the hazard ratios from GOG-0179 for topotecan survival and hazard ratios from the meta-analysis for the cisplatin survival curves, and assuming maximum wastage, the ICER for topotecan plus cisplatin was £30,171 per QALY gained in comparison with cisplatin alone and £11,627 in comparison with paclitaxel plus cisplatin. If minimum wastage of topotecan was assumed, the ICER was £23,586 per QALY gained in comparison with cisplatin alone and £1270 in comparison with paclitaxel plus cisplatin.

3.30 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/TAxxx

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of topotecan, having considered evidence on the nature of recurrent and stage IVB cervical cancer and the value placed on the benefits of topotecan by women with

the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.2 The Committee considered current clinical practice for treating recurrent and stage IVB cervical cancer. The Committee heard from clinical specialists that there is currently no nationally agreed standard treatment for women with this condition. Treatment may consist of topotecan plus cisplatin, cisplatin alone, or paclitaxel plus either carboplatin or cisplatin. The clinical specialists considered that combination therapies were generally more effective than single-agent therapies. They also stated that the main reason for there being no single established treatment regimen is because clinical trials in the past had not shown clinically significant advantages in terms of response rates or overall survival for any single regimen in this patient group. The Committee heard from patient experts that they considered it was important to have a number of treatment options because one may be more suitable than others for the individual patient. For example, the choice of treatment may be influenced by comorbidities such as renal dysfunction. Patient experts also highlighted that for some women topotecan plus cisplatin may be considered a final treatment option.

4.3 The Committee specifically considered the use of cisplatin to treat recurrent and stage IVB cervical cancer. It heard from clinical specialists that approximately 90–95% of women within the licensed population will have previously received cisplatin because it is standard UK clinical practice to use cisplatin either with radiotherapy or as chemotherapy alone as first-line treatment for cervical cancer. It heard how cervical screening in the UK enables early identification of disease and so initial presentation with stage IVB disease is unusual. The Committee also heard that the dose of

cisplatin used in chemotherapy and in chemoradiotherapy is the same.

4.4 The Committee heard from clinical specialists that previous cisplatin use has a significant effect on response rates to subsequent cisplatin-containing chemotherapy regimens. In cisplatin-naive women, response rates to cisplatin were approximately 45%, which could be higher if combination therapy was used. However, for women who had previously received cisplatin, response rates could be as low as 10%. In addition, the response rates were found to increase as the duration of remission after initial cisplatin treatment increased.

4.5 The Committee discussed the clinical effectiveness of topotecan plus cisplatin compared with cisplatin alone presented in the main trial. The Committee considered that combination therapy was shown to be more effective than cisplatin alone in the GOG-0179 trial population. The Committee noted the results from the subgroup analyses suggesting that topotecan plus cisplatin was more clinically effective in women who were cisplatin naive than in women who had previously received cisplatin. The Committee considered that the reduced response to topotecan plus cisplatin was evident even when the sustained cisplatin-free interval was longer than 180 days.

4.6 The Committee examined the trial comparing four combination treatments (GOG-0204), including topotecan plus cisplatin. The Committee was aware that the trial had closed early because none of the other treatment combinations were likely to show a significant benefit over paclitaxel plus cisplatin. The Committee noted that hazard ratios from this trial suggested that paclitaxel plus cisplatin was more effective than the other cisplatin combination therapies, but this difference did not reach statistical significance.

The Committee heard from clinical specialists that they did not consider there to be any differences in effectiveness between the different combinations that had been used in this trial. The Committee noted that in this trial approximately 70% of women had received cisplatin as prior chemoradiotherapy. The Committee understood that no specific data for cisplatin-naive women from this trial had been provided. It noted that the manufacturer had also included an indirect comparison of topotecan plus cisplatin with paclitaxel plus cisplatin. The Committee recognised that this comparison suggested that topotecan plus cisplatin was more effective than paclitaxel plus cisplatin, but again the difference did not reach statistical significance. The Committee concluded that there was uncertainty about the differences in effectiveness among combination chemotherapy regimens.

4.7 When considering the comparative evidence the Committee was aware that there were differences in the trial populations. The Committee considered that the trial of combination therapies (GOG-0204) appropriately reflected the majority of the clinical population in England and Wales, where women often received chemoradiotherapy that included cisplatin. However, the Committee noted that for the subgroup of women who were cisplatin naive, the trial of combination therapies was not representative of this population. The Committee concluded that there was additional uncertainty about the efficacy of topotecan in comparison with paclitaxel and other combination regimens for this subgroup.

4.8 The Committee discussed the manufacturer's network meta-analysis that was provided after consultation on the appraisal consultation document. The Committee noted that the meta-analysis combined direct and indirect evidence that, when considered individually, did not show consistent effects. In addition,

there were differences in the trial populations in terms of prior cisplatin exposure, performance status and disease stage. The Committee heard from the ERG that they did not consider that the data from the trials were exchangeable, and therefore it was inappropriate to carry out a meta-analysis of the data. The Committee also heard from the ERG that the manufacturer's analyses that pooled the data for paclitaxel suggested an estimate of effect similar for both the licensed population and the cisplatin-naive population that was not consistent with the clinical trial or clinical specialists' evidence or biological plausibility. The Committee concluded that in principle a network meta-analysis was an appropriate method of calculating efficacy, but the nature of the evidence available in this situation meant that it could not be considered appropriate as a basis on which to make a decision about the cost effectiveness of topotecan.

4.9 The Committee considered the adverse event profile of topotecan and recognised that women receiving topotecan plus cisplatin may have more adverse events compared with those receiving cisplatin alone. The Committee heard from clinical specialists specifically about neutropenia and febrile neutropenia. It heard how febrile neutropenia may lead to hospital admission, and may be a more frequent occurrence than for other regimens such as paclitaxel plus cisplatin. However, patient experts mentioned that they considered the safety profile of topotecan plus cisplatin to be manageable, although they were concerned about reported deaths following chemotherapy. They also indicated that quality of life may not be worse for women receiving combination therapy than for women receiving monotherapy, although they were specifically concerned about fatigue.

Cost effectiveness

4.10 The Committee considered the evidence on the cost effectiveness of topotecan plus cisplatin presented in the manufacturer's submission. The Committee recognised that the manufacturer considered their main analysis to be the within-trial comparison and not the model-based comparison. The Committee noted that the ERG could not completely validate the within-trial comparison and that they considered the manufacturer's model-based comparison to have greater external validity. The ERG had therefore used the model-based comparison as the basis for their exploratory analyses.

4.11 The Committee noted that in the within-trial comparison the base-case ICER provided by the manufacturer for topotecan plus cisplatin compared with cisplatin alone was £18,000 per QALY gained in the licensed population, £11,000 per QALY gained in the cisplatin-naive population and £32,500 per QALY gained in the sustained cisplatin-free interval population. The Committee noted that the results of the model-based comparison using the hazard ratio derived from the indirect comparison suggested that topotecan plus cisplatin had greater efficacy and lower costs than paclitaxel plus cisplatin. However, when the hazard ratio from the trial comparing different combination therapies directly was used, paclitaxel plus cisplatin was more effective and less costly than topotecan plus cisplatin.

4.12 The Committee considered the utility estimates provided by the manufacturer. The Committee heard from the ERG that the manufacturer had incorrectly mapped disease-specific quality of life to utility and that correcting this led to a lower starting utility of 0.72 instead of 0.79. The ERG also expressed concerns about the mapping equation used in the base-case analysis, including the

transparency of the analysis and imputation methods. The ERG suggested that combining their amended starting utility from the main clinical trial with data identified by the manufacturer from a study of metastatic breast cancer could be more appropriate. The Committee recognised that neither approach to estimating utilities reflected the reference case and considered that both sets of utility estimates were associated with uncertainty. However, on balance the Committee considered that utility values suggested by the ERG, which led to more favourable ICERs, may be more appropriate than those provided by the manufacturer.

4.13 The Committee considered the manufacturer's assumptions about the number of topotecan vials required in clinical practice and the administration costs. The Committee heard that the manufacturer may have underestimated the administration costs for topotecan on days 2 and 3 because they had used an assessment report from a previous appraisal that had built up the costs without the appropriate health resource group codes being available. The ERG stated that these codes were now available and that the cost for administering the second and third infusion of topotecan would be £195 rather than £51. The Committee considered that the revised administration costs proposed by the ERG were appropriate. The Committee also heard from the ERG that the manufacturer had not assumed minimum or maximum wastage of excess topotecan, but used a midpoint. The ERG considered that an assumption of maximum wastage may be more consistent with the SPC. The Committee heard from clinical specialists that although women were grouped so that drug wastage could be reduced, there was less opportunity to group women receiving topotecan because of the small number of women who receive the drug. The Committee considered that although there was uncertainty about the

manufacturer's estimate of topotecan wastage, assumptions of either minimum or maximum wastage may also not be accurate.

4.14 The Committee noted that there appeared to be inconsistencies between the mean cost estimates in the within-trial comparison and the model-based comparison. The Committee heard from the ERG that this may be because dose reduction related to adverse events was included in the within-trial comparison but not in the model-based comparison. However, without a breakdown of costs, the ERG was unable to confirm this. In addition, there were no data on how the use of paclitaxel may be affected by dose reduction. The Committee considered that dose reduction could be important and the ERG's exploratory analyses showed that dose reduction could lower the ICER. However, the Committee was not persuaded that the cost estimates including dose reduction were sufficiently robust for these to form the basis of their examination of the cost effectiveness of topotecan.

4.15 The Committee considered how adverse events had been included in the model-based comparison. The Committee heard from clinical specialists that the manufacturer's assumption that an adverse event lasted only a week was appropriate. The Committee noted that only the most severe adverse event was taken into account in the manufacturer's analysis even if two or more adverse events were experienced concurrently. The clinical specialists agreed that there may be a further negative impact on quality of life for women who have two concurrent adverse events. Overall the Committee considered that the manufacturer may have underestimated the reduction in quality of life associated with multiple adverse events.

4.16 The Committee first considered the fully incremental exploratory analysis for the licensed population undertaken by the ERG that incorporated amended administration costs and utility values. The

Committee noted that, for the licensed population, using the hazard ratio from the indirect comparison, the ICER for topotecan plus cisplatin compared with cisplatin alone was £59,000 per QALY gained when minimum wastage was assumed, and the ICER for topotecan plus cisplatin compared with paclitaxel plus cisplatin was £117,000 per QALY gained when maximum wastage was assumed. The Committee was also aware that when the hazard ratio derived from the trial of different combination therapies was used, topotecan plus cisplatin was dominated by paclitaxel plus cisplatin. The Committee considered that the trial of different combination therapies (GOG-0204) was more representative of the patient population in England and Wales than the other available evidence. The Committee therefore concluded that for the licensed population, the cost-effectiveness data suggested that topotecan in combination with cisplatin was not a cost-effective use of NHS resources.

4.17 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments which may extend the life of patients with a short life expectancy and which 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 into account the Committee must be persuaded that the estimates of the extension to life are robust and the assumptions used in the reference-case economic modelling are plausible, objective and robust.

4.18 The Committee considered that the life expectancy for women with recurrent and stage IVB cervical cancer would normally be less than 24 months. The Committee noted that topotecan was licensed for multiple indications, but it could still be considered to be indicated for a small patient population. The Committee discussed the additional benefits provided by topotecan in comparison with other therapies available on the NHS. It noted the clinical trial results from GOG-0179 and agreed that for the licensed population topotecan plus cisplatin had demonstrated a gain in life expectancy of more than 3 months in comparison with cisplatin alone. However, the Committee was aware that the majority of women receive combination therapies in the NHS. The Committee noted the results of the trial of combination therapies (GOG-0204), which had closed early because none of the treatments including topotecan were likely to show a significant benefit over paclitaxel plus cisplatin. The Committee also noted the clinical specialists' comments that they considered there to be equal efficacy among the different combination treatments in GOG-0204. On balance, the Committee considered that, for the licensed population, topotecan plus cisplatin compared with other combination therapies currently available in the NHS had not shown an additional benefit of 3 months. The Committee therefore concluded that topotecan plus cisplatin did not fulfil the criteria for consideration of NICE's supplementary advice on end of life and agreed that topotecan in combination with cisplatin could not be recommended as a cost-effective use of NHS resources.

4.19 The Committee then considered the subgroup of women who had not previously received cisplatin. The Committee noted that the manufacturer's estimates suggested topotecan plus cisplatin may be cost effective in this group. The Committee considered the ERG's exploratory analyses for this subgroup. When the hazard ratios from the indirect comparison were used the ICER for topotecan plus cisplatin compared with cisplatin alone was £26,800 per QALY gained assuming minimum wastage, and £34,000 per QALY gained assuming maximum wastage. The Committee recognised that this did not include dose reduction, which the ERG had suggested could further reduce these ICERs. The Committee was aware that when the hazard ratios from the trial of different combination therapies were used, topotecan plus cisplatin was dominated by paclitaxel plus cisplatin, but that this evidence was predominantly from a population who had received cisplatin as a radiosensitiser before. Because the indirect comparison was the only data available in which the majority of women were cisplatin naive, the Committee was persuaded that topotecan plus cisplatin could be considered an appropriate use of NHS resources for the treatment of women who have not previously received cisplatin.

4.20 In light of the duty to have due regard to the need to eliminate unlawful discrimination and promote equality, the Committee discussed the higher prevalence of cervical cancer among women living in the most socioeconomically deprived areas, as outlined by the patient expert statements. It also discussed comments received during consultation on the appraisal consultation document. The Committee noted that a negative recommendation for topotecan in combination with cisplatin for the group of women with prior exposure to cisplatin does not impact particularly on any group protected by the equalities legislation. In addition, given the uncertainty about whether topotecan in combination with cisplatin is

more clinically effective than other combination therapies for the treatment of cervical cancer in women with prior exposure to cisplatin, and the availability of alternative treatment options, the Committee was satisfied that its recommendation was consistent with NICE's obligations under the equalities legislation and the requirement for fairness.

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 that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Published

- High dose rate brachytherapy for carcinoma of the cervix. NICE interventional procedure guidance 160 (2006). Available from www.nice.org.uk/IPG160
- Guidance on the use of liquid-based cytology for cervical screening (review). NICE technology appraisal guidance 69 (2003). Available from www.nice.org.uk/TA69

7 Review of guidance

7.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive in September 2012. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

David Barnett
Chair, Appraisal Committee
September 2009

Appendix A: Appraisal Committee members 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.

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Professor Philip Home (Vice Chair)

Professor of Diabetes Medicine, Newcastle University

Dr Amanda Adler

Consultant Physician, Cambridge University Hospitals Trust

Professor A E Ades

MRC Senior Scientist, MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol

Dr Tom Aslan

General Practitioner, Stockwell, London

Dr Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Dr Paul Ewings

Statistician, Taunton & Somerset NHS Trust, Taunton

Mr Adrian Griffin

VP Strategic Affairs, LifeScan, Johnson & Johnson

Dr Alec Miners

Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Dr Ann Richardson

Lay Member

Mrs Angela Schofield

Chairman, Bournemouth and Poole Teaching PCT

Mr David Thomson

Lay Member

Mr William Turner

Consultant Urologist, Addenbrooke's Hospital

Mr Mike Spencer

General Manager, Cardiff and Vale NHS Trust – Facilities and Clinical Support Services

Dr Jane Adam

Department of Diagnostic Radiology, St George's Hospital

Professor Karl Claxton

Professor of Health Economics, University of York

Dr David Newsham

Lecturer (Orthoptics), University of Liverpool

Professor Iain Squire

Consultant Physician, University Hospitals of Leicester

Dr James Moon

Consultant Cardiologist and Senior Lecturer, University College London Hospital (UCLH) and UCL

Dr Ian Lewin

Consultant Endocrinologist, North Devon District Hospital

Mr Christopher Earl

Surgical Care Practitioner, Renal Transplant Unit, Manchester Royal Infirmary

Dr Simon Dixon

Reader in Health Economics, University of Sheffield

Mrs Eleanor Grey

Lay Member

Dr Peter Heywood

Consultant Neurologist, Frenchay Hospital

Mrs Elizabeth Brain

Lay Member

B 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.

Dr Andres Roman

Technical Lead

Zoe Garrett

Technical Adviser

Bijal Joshi

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by the Centre for Reviews and Dissemination (CRD), Centre for Health Economics (CHE), The University of York:

- Paton F et al. Topotecan for the treatment of recurrent and stage IVB carcinoma of the cervix, April 2009

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

I Manufacturer/sponsor:

- GlaxoSmithKline (topotecan)

II Professional/specialist and patient/carer groups:

- Cancer Research UK
- Jo's Trust
- Rarer Cancers Forum
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- Royal College of Radiologists
- United Kingdom Oncology Nursing Society

III Other consultees

- Department of Health
- Welsh Assembly Government

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

- Centre for Reviews and Dissemination, Centre for Health Economics, The University of York
- Department of Health, Social Services and Public Safety for Northern Ireland
- National Collaborating Centre for Cancer
- National Institute for Health Research Health Technology Assessment Programme
- NHS Quality Improvement Scotland
- Pfizer

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on topotecan for the treatment of recurrent and stage IVB carcinoma of the cervix by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Lynn Hirschowitz – Consultant Gynaecological Pathologist, nominated by The Royal College of Pathologists – clinical specialist
- Dr Paul Symonds – Reader in Oncology/Consultant Oncologist, nominated by The Royal College of Physicians – clinical specialist
- Ms Catherine Oakley – Chemotherapy Nurse Consultant, nominated by United Kingdom Oncology Nursing Society – clinical specialist
- Ms Stella Pendleton - Executive Director, nominated by Rarer Cancers Forum – patient expert