NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Topotecan for the treatment of recurrent and stage IVB carcinoma of the cervix

Premeeting briefing

This briefing presents major issues arising from the manufacturer's submission (MS), Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that although condensed summary information is included for ease of reference, this briefing should be read in conjunction with the full supporting documents.

The manufacturer was asked to provide further information on clinical and cost-effectiveness issues, including:

- **details of the search strategies used to identify the cost-effectiveness and clinical-effectiveness evidence**
- **the rationale for including trials in the manufacturer's submission, including exclusion and inclusion criteria**
- **information on patient characteristics, trial design, quality-of-life, and adverse events from the GOG-179 and GOG 169 clinical trials**
- **details of trial GOG-0204 and the rationale for not formally including it in the indirect comparison**
- **information on how the utilities were derived in the cost-effectiveness analyses**
- **information on cost data used in the economic model**
- **revised cost-effectiveness analyses for the indirect comparison incorporating a longer time horizon, progression-free survival data and utility data, to provide a cost-per-quality-adjusted life year (QALY) analysis.**

Licensed indication

Topotecan (Hycamtin, GlaxoSmithKline) in combination with cisplatin is indicated for patients with carcinoma of the cervix recurrent after radiotherapy and for patients with stage IVB disease. Patients with prior exposure to

cisplatin require a sustained treatment-free interval to justify treatment with the combination.

Key issues for consideration

Clinical effectiveness

- What does the Committee consider to be the most appropriate comparators to reflect current standard treatment for women with recurrent and stage IVB cervical carcinoma in England and Wales?
- What is the Committee's opinion of the role of cisplatin in the treatment pathway of cervical cancer and how previous exposure to cisplatin affects treatment with topotecan?
- Does the Committee consider that the manufacturer has identified all relevant evidence in their submission, taking current clinical practice in England and Wales into account?
- Does the Committee consider that the trials are representative of the population of women with recurrent and stage IVB cervical carcinoma in England and Wales?
- Does the Committee consider that the subgroups of women identified by the manufacturer from the trial data reflect the patient population in England and Wales?
- What does the Committee consider to be the importance of trial GOG-204? Does the Committee accept the manufacturer's justification for not including it formally in their submission?
- What is the Committee's opinion of the indirect comparison analysis carried out by the manufacturer?
- Does the Committee consider that the trials used in the indirect comparisons are sufficiently comparable to provide robust estimates of the clinical effectiveness of topotecan?
- What is the Committee's opinion of the adverse event profile of topotecan?

Cost effectiveness

- What is the Committee's opinion of a trial-based analysis to determine the cost effectiveness of topotecan plus cisplatin compared with cisplatin alone?
- What is the Committee's assessment of the internal and external validity of the SAS analysis?
- What is the Committee's assessment of the internal and external validity of the cost-effectiveness analysis undertaken in Excel?
- In the economic analyses, what does the Committee consider to be appropriate assumptions and estimates for the inputs to the model, for wastage of topotecan, administration costs of topotecan, utilities, costs of adverse events and dose reduction during treatment?
- For the cost-effectiveness analysis of the comparison of topotecan plus cisplatin with paclitaxel plus cisplatin, does the Committee consider the direct, indirect or pooled (including both direct and indirect evidence) estimate of clinical effectiveness to be the most appropriate?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	Women with carcinoma of the cervix recurring after radiotherapy and women newly presenting with stage IVB disease. Women with prior exposure to cisplatin required a sustained treatment-free interval to justify treatment with the combination. The duration of the cisplatin-free interval was assumed to be at least 180 days, consistent with analyses presented in the summary of product characteristics (SPC). In addition to the licensed population, the manufacturer included the following subgroups: • licensed population excluding stage IVB women • cisplatin-naive population • stage IVB women (by definition cisplatin-naive, as they are newly presenting) • cisplatin-naive recurrent population • women with a sustained cisplatin-free interval (SCFI) of more than180 days. The manufacturer highlighted that after breast cancer, cervical cancer is the most common cancer in women less than 35 years.
Intervention	Topotecan plus cisplatin, administered intravenously for 6 courses or until disease progresses.
Comparators	The comparators included platinum alone (for example cisplatin) and in combination with other treatments (for example paclitaxel in combination with cisplatin).
Outcomes	The primary outcome was overall survival. Secondary outcomes included progression-free survival, response rates (complete response and partial response), adverse effects of treatment, and health-related quality-of-life (FACT-G).
Economic evaluation	The submission included two analyses. The first was a patient-level analysis, including a direct comparison of topotecan plus cisplatin in comparison with cisplatin alone. This analysis was based on the key clinical study. The second was an indirect analysis of topotecan plus cisplatin compared with paclitaxel plus cisplatin.

1.2 Evidence Review Group comments

1.2.1 Population

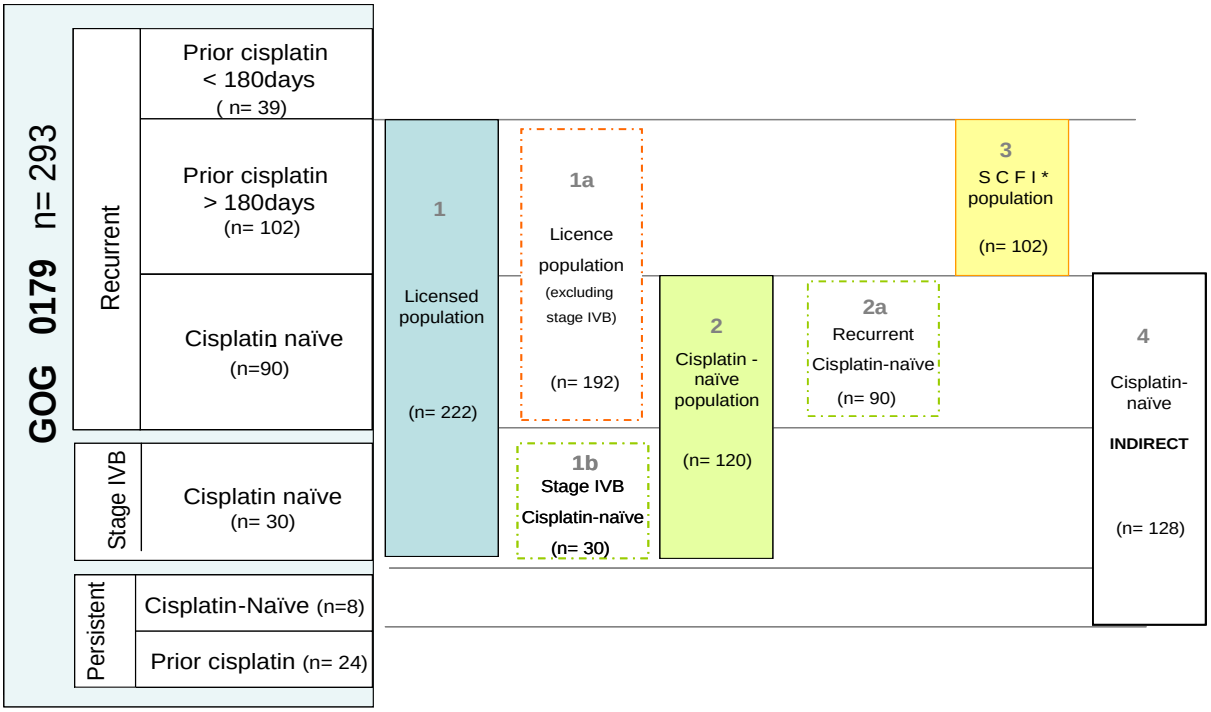
The ERG stated that the manufacturer's submission considered the licensed population. Direct evidence came from a clinical trial comparing topotecan plus cisplatin with cisplatin monotherapy in a population which included the licensed population, as well as patients with persistent disease and those who had received prior cisplatin based chemotherapy within 180 days. Indirect evidence came from another trial comparing paclitaxel plus cisplatin with cisplatin monotherapy in a population which also included patients with persistent disease (outside the licensed population) but excluded patients who had received prior chemotherapy (some of whom would be within the licensed population).

The ERG noted that the MS included clinical management data from the IMS Oncology Analyzer database to identify current standard care. The population identified in the database was mainly women with stage IV disease, but not limited to stage IVB. The database included only a small number of women who had recurrent disease and who had received chemotherapy after radiotherapy, or who had received chemotherapy after non-cisplatin chemoradiotherapy. The ERG observed that none of the women in the IMS database with recurrent disease had received previous chemotherapy more than 180 days after receiving cisplatin-based chemoradiotherapy. The ERG raised concerns about whether the population in the IMS database was similar to the population included in the trials in the MS, and which was more representative of the patient population in England and Wales.

The ERG raised queries about the use of cisplatin as a radiosensitiser and potential differences in the use of cisplatin as a radiosensitiser in clinical practice and in the clinical trials. The ERG considered that this may also affect the extent to which the population in the clinical trials could be considered

representative of women with recurrent and stage IVB cervical carcinoma in England and Wales.

Figure 1 Schematic of study population and subgroups analysed in the manufacturer's submission.



1.2.1 Intervention

The ERG noted that the summary of product characteristics (SPC) states that topotecan should be administered in combination with cisplatin. The recommended dosage schedule is 0.75 mg/m^2/day topotecan, administered as a 30-minute intravenous infusion on days one, two and three, with a dose of 50 mg/m^2/day cisplatin administered after topotecan on day one. Treatment should be repeated every 21 days for six courses 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/litre, and the haemoglobin level is at least 9g/100 ml (after transfusion if necessary).

1.2.2 Comparators

The MS included data from the IMS database and identified cisplatin as the most relevant comparator (MS, page 11). The ERG noted that clinicians consulted by the manufacturer confirmed the pattern of treatment identified by the IMS database, but stated that paclitaxel in combination with cisplatin may be used more than suggested. Paclitaxel in combination with cisplatin was included as a second comparator in the MS.

The ERG highlighted that according to the IMS data, carboplatin plus paclitaxel appeared to be the second most frequently used treatment in the patient population. According to the ERG's clinical adviser, carboplatin plus paclitaxel may be better tolerated than cisplatin and may produce better response rates. The manufacturer justified excluding this combination as a comparator because of the limited evidence available.

The ERG stated that the manufacturer's reason for not including other treatments such as cisplatin plus 5-fluorouracil (5-FU) and cisplatin plus mitoxantrone, which were also identified by the IMS database, was not clearly justified.

1.2.3 Outcomes

The ERG stated that the outcomes considered in the MS reflected those in the final scope issued by NICE.

The ERG stated that overall survival (OS) was the primary outcome, and was defined as the time from randomisation until death in the intention-to-treat (ITT) population, or until date of last contact, for women who were still alive at this point. Progression-free survival (PFS) was defined as the minimum amount of time from randomisation until clinical progression, death, or date of last contact. The ERG's clinical adviser highlighted the importance of PFS for the patient population.

The ERG stated that response rates, quality of life (QoL) and adverse events were the secondary outcomes in the main trial (GOG-0179). Response rate was defined as the number of patients responding to treatment (either complete response or partial response) divided by the number of patients in each respective treatment group in the intention-to-treat population. Quality of life was assessed using the Functional Assessment of Cancer Therapy – Cervix Cancer (FACT-Cx), FACT-G (general), FACT-NTX (neurotoxicity), Brief Pain Inventory (BPI), and UNISCALE.

1.2.4 Economic evaluation

Incremental cost per quality-adjusted life year (QALY) gained was used as a measure of cost effectiveness, which is in accordance with the NICE reference case. The ERG noted concerns with the time horizon (24 months) used in the economic model for the indirect comparison. The manufacturer subsequently amended the model to include a longer time horizon (36 months).

1.3 Statements from professional/patient groups and nominated experts

Clinical specialists stated that there were no specific guidelines about treatment for the small group of women with diverse clinical presentations of advanced carcinoma of the cervix. In their opinion there seems to be wide variation in treatment, and treatment options are limited by previous administration of chemotherapy and/or radiotherapy. The use of topotecan for treating recurrent and stage IVB carcinoma of the cervix required scrutiny and comment by clinical oncologists and specialist nurses, particularly in relation to current practice, treatment options, risks and benefits and prognosis.

Patient experts stated that statistics from Cancer Research UK showed that women living in the most deprived areas have rates of cervical carcinoma more than three times higher than those in the least deprived areas. In

addition, patient experts noted that a direct link had been demonstrated between social class and cervical carcinoma.

Patient experts also stated that recurrent and stage IV carcinoma of the cervix may be challenging to manage because the disease is often unrelenting but relatively slow growing. They noted that pelvic pain from the disease can frequently be hard to control and that women may have to bear this pain for a long time. The disease can also cause profuse vaginal discharge and fistulation from the bowel and/or bladder into the vagina.

Patient experts stated that chemotherapy would need to be given at specialist cancer centres under the care of a gynaecological cancer multidisciplinary team. Topotecan is already used in a gynaecological cancer setting, for the treatment of ovarian cancer. Healthcare professionals are familiar with the treatment. Patient experts also noted that fitness for chemotherapy may be impaired when cervical carcinoma affects the renal system and requires interventions such as ureteric stenting. However, such interventions may be required regardless of the chemotherapy regimen provided.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

A systematic review by the manufacturer identified two clinical trials of topotecan. The first study was a phase III randomised controlled clinical trial in which topotecan plus cisplatin was compared with cisplatin alone (GOG-0179). GOG-0179 was an independent trial including 293 women with stage IVB, recurrent or persistent carcinoma of the cervix unsuitable for curative treatment with surgery and/or radiotherapy. This study was used as the main clinical evidence source in the MS. The study results demonstrated that topotecan in combination with cisplatin led to a benefit in overall survival in comparison with cisplatin alone. Median overall survival was 9.40 and 6.54 months respectively (HR 0.76, 95% CI: 0.59 to 0.98 p = 0.03). Similar benefits

were observed for progression free survival; 4.57 and 2.91 months respectively (HR 0.76, 95% CI: 0.60 to 0.97, p=0.03). The overall survival results for key subgroups of the trial are shown in table 1. Progression free survival subgroup data are shown in table 15 of the manufacturer's response to the clarification letter (page 21)

Table 1 Overall survival: GOG-0179 key subgroup analyses (MS page 58).

	Licenced population		**Cisplatin-naive population**		**Sustained cisplatin-free interval (SCFI) population**		**Cisplatin-naive (for indirect analysis [IND]) population**	
	Cisplatin (n = 115)	Topotecan plus cisplatin (n = 107)	Cisplatin (n = 62)	Topotecan plus cisplatin (n = 58)	Cisplatin (n = 53)	Topotecan plus cisplatin (n = 49)	Cisplatin (n = 64)	Topotecan plus cisplatin (n = 64)
Overall survival time (months)								
Mean	9.93	12.95	11.1	15.1	7.95	9.54	11.1	14.4
Median	7.3	11.9	8.5	14.5	6.3	9.9	8.5	12.5
95% CI*	6.0–9.5	9.4–13.7	6.4–11.1	11.5–17.5	4.9–9.5	7.0–12.6	6.5–11.3	9.2–17.4
Log rank p-value	0.0041		0.0098		0.1912		0.0206	
Hazard ratio (95% CI)	0.652 (0.485, 0.875)		0.587 (0.389, 0.884)		0.75 (0.492, 1.155)		0.633 (0.428, 0.935)	

* Confidence interval for median OS

The manufacturer identified an additional trial of topotecan plus cisplatin that was not formally included in the clinical-effectiveness review. GOG-0204 was a randomised controlled clinical trial reported as an abstract, which included a head-to-head comparison of four cisplatin combinations containing (paclitaxel (n=103), vinorelbine (n=108), gemcitabine (n=112) and topotecan (n=111)). Patients who had received prior chemotherapy were excluded, unless this was concurrent with radiation, and approximately 70% of included patients had previously received cisplatin as a radiosensitiser. A planned interim analysis recommended early closure of GOG-0204 as the other comparator groups were unlikely to demonstrate statistically significant benefit when compared to paclitaxel plus cisplatin. The manufacturer stated that an additional limitation of this trial was that the majority of women (55% in the paclitaxel arm, 53% in the topotecan arm) were of performance status 0, with

no women of performance status 2 included. They argued that this status was not representative of the overall patient population.

The results for GOG-0204 are shown in table 2 below and in table 4.2.2.1 of the ERG report (page 36). GOG-0204 also demonstrated a non-significant trend for quality-of-life, response rate and PFS in favour of paclitaxel plus cisplatin.

Table 2 Treatment hazard ratios for progression-free and overall survival comparing cisplatin plus paclitaxel versus other cisplatin combination treatment (GOG-0204).

	Cisplatin + vinorelbine vs Cisplatin + paclitaxel	**Cisplatin + gemcitabine vs Cisplatin + paclitaxel**	**Cisplatin + topotecan vs Cisplatin + paclitaxel**
Relative hazard ratio PFS (Var(ln(HR))	1.357 (0.020)	1.394 (0.021)	1.268 (0.021)
Relative hazard ratio OS (Var(ln(HR))	1.147 (0.026)	1.322 (0.025)	1.255 (0.025)

Indirect comparison

The manufacturer identified one clinical trial that compared cisplatin plus paclitaxel with cisplatin alone (GOG-0169). This was used in an indirect analysis with GOG-0179. GOG-0169 was a phase III trial that compared paclitaxel plus cisplatin (n = 130) with cisplatin alone (n = 134) in women with stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix. Unlike GOG-0179, GOG-0169 excluded patients with prior chemotherapy, unless this was used for radiation sensitisation, and therefore differences existed in the proportion of patients who had received prior chemoradiation therapy in the two trials. Overall, 71 women had received chemotherapy plus radiation as primary treatment for cervical carcinoma, including 40 (30%) women in the cisplatin group and 31 (24%) women in the paclitaxel plus cisplatin group. Cisplatin was only one of four chemotherapeutic agents (cisplatin, fluorouracil, hydroxyurea, and navelbine) used alone or in combination as a radiation sensitiser. The results for this study are given in table 3. GOG-0169 did not report the hazard ratio for overall survival,

therefore the manufacturer estimated the hazard ratio (HR = 0.87 favouring paclitaxel plus cisplatin) from the survival curves using the Parmar (1998) methodology.

Table 3 Summary of efficacy outcomes; GOG-0169, ITT population (MS page 63).

Outcome	Cisplatin (n = 134)	Paclitaxel plus cisplatin (n = 130)	p-value
Median overall survival (months)	8.8	9.7	ns
Median PFS survival (months)	2.8	4.8	<0.001

The indirect comparison analysis was performed in Excel using the hazard ratios for mean overall survival in the two studies. The manufacturer argued that age, performance status, histological grade and number of cycles were broadly similar for women in GOG-0169 compared with those in the cisplatin-naive population in GOG-0179, including those with persistent disease. Therefore the indirect comparison was completed only for that group of patients (shown as subgroup 4 in figure 1). The indirect analysis generated a further hazard ratio statistic, 0.72, together with confidence intervals (see table 4).

Table 4 Results of indirect comparison between GOG-0179 (cisplatin-naive population) and GOG-0169 (ITT population) (MS page 67)

Study	Regimen	n	Hazard ratio	Lower CI	Upper CI
GOG-179	Cisplatin	64	0.63	0.43	0.94
	Topotecan in combination with cisplatin	64			
GOG-169	Cisplatin	134	0.87	0.68	1.11
	Paclitaxel in combination with cisplatin	130			
Hazard ratio of the compared trials					
GOG-0179+GOG-0169	Topotecan in combination with cisplatin		0.72	0.46	1.15
	Paclitaxel in combination with cisplatin				
CI: confidence interval					

2.2 Evidence Review Group comments

The ERG did not consider that the MS included all of the evidence available that may have informed indirect comparisons. The ERG was unable to reproduce the search strategies provided and did not consider that the inclusion and exclusion of studies was sufficiently justified.

The ERG noted that the main randomised controlled trial (GOG-0179) seemed to be well conducted, but another direct comparison (GOG-0204) was not formally included in the analysis. The ERG considered that the evidence submitted suggested that in general, combination chemotherapy was more effective than single agent chemotherapy, but that this conclusion was uncertain because of limited evidence, and the uncertainties surrounding key issues, such as the the low response rates with cisplatin monotherapy, and the handling and reporting of quality of life data and whether the results are representative of the whole patient experience. The ERG noted that the subgroup analyses by the manufacturer suggested that previous cisplatin use may modify the effect of combination treatment with topotecan plus cisplatin.

The ERG also considered that the indirect comparison may be subject to uncertainty because of the different populations enrolled in each of the clinical trials (see table 3.2.1 of the ERG report, page 18). The ERG expressed concerns about how representative of clinical practice the population in the trials were, specifically highlighting the use of cisplatin as a radiosensitiser.

The ERG considered that the omission of trials from the network of evidence (including GOG-0204) limited the number of available comparators and meant that the evidence base was smaller than potentially it could have been. The ERG did not consider that the rationale for the exclusion of trials based on the treatments not being licensed in the patient population was justified. The ERG highlighted the differing conclusions about the clinical effectiveness of topotecan plus cisplatin in comparison with paclitaxel plus cisplatin obtained from the indirect comparison of GOG-0169 and GOG-0179 and the direct comparison in GOG-0204.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer submitted two economic evaluations. The first was a trial-based direct comparison of topotecan plus cisplatin with cisplatin alone using a time horizon of 36 months. This analysis was based on individual patient-level data from the GOG-0179 trial and data for clinical efficacy, safety and quality of life used in the analysis were derived directly from the trial. Information on resource use was derived from clinical events occurring in the trial supplemented by data from external sources including expert opinion. Unit cost data were obtained from published sources including national reference costs. Separate analyses were undertaken for the main licensed population as well as subgroups, including both cisplatin-naive and sustained cisplatin-free interval populations.

The second economic evaluation was undertaken in Excel, and compared topotecan plus cisplatin with paclitaxel plus cisplatin using a time horizon of 24

months. The main analysis was based on aggregate data derived from the indirect comparison of the GOG-0179 and GOG-0169 trials. However, an additional sensitivity analysis also included direct data on this comparison from the GOG-0204 trial. The manufacturer stated because patient level data were not available for GOG-0169 the most appropriate, least potentially biased comparison would be between the overall ITT population of GOG-0169 and the cisplatin-naive population of GOG-0179 including patients with persistent disease (MS page 85). Resource use in the indirect comparison was based on the costing algorithms developed for the direct analysis. The indirect comparison presented within the MS expressed results in terms of life-years gained. In response to a request from the ERG, an additional indirect analysis was presented expressing outcomes in terms of both life-years and QALYs gained.

The trial-based direct comparison was considered by the manufacturer to be the primary analysis within their submission. Justification for the choice of a patient-level analysis as the main evaluation was provided in response to a query by the ERG (see appendix 1 of the response to clarification). The Excel-based indirect comparison was provided in order to link to alternative comparators used in England and Wales, although the potential shortcomings considered by the manufacturer about this approach meant that this was presented as a secondary analysis.

Quality-of-life benefits were incorporated into the direct comparison analysis by an algorithm linking a disease-specific measure of quality of life (FACT-G) to utility (page 104 of the MS). An alternative source of utility data was included in a sensitivity analysis based on a review of the cervical cancer literature and other gynecological cancer (including breast cancer) literature reporting utility values (page 107 of the MS). The values used in the sensitivity analysis were based on a study by Brown (1998) that considered the health state utilities of women with breast cancer using a proxy population. Utility values were not included in the indirect comparison model in the manufacturer's submission. These were subsequently included in response to

the clarification question using the utility values from the Brown study (page 28 of the manufacturer's response to the clarification letter).

Direct comparison with cisplatin

Deterministic cost-effectiveness results for the licensed population are shown in table 5. Probabilistic sensitivity analysis shows that on more than 50% of occasions the incremental cost-effectiveness ratio (ICER) was below £20,000 per QALY gained and on 88% of occasions was below £30,000 per QALY gained.

Table 5 Deterministic cost-effectiveness results from the MS for the licensed population – direct comparison.

Treatment arm	Mean costs*	Mean QALYs (LYs)*	Incremental cost	Incremental QALYs (LYs)	Cost/QALY (Cost/LYG)
Topotecan + cisplatin	£6074	0.83 (1.12)	£4122	0.23 (0.27)	**£17,974 (£15,091)**
Cisplatin	£1952	0.60 (0.84)			

*All costs and outcomes discounted at 3.5% per annum. LYs = life years, LYG = life-years gained, QALY = quality-adjusted life year

Subgroups in the direct comparison

The manufacturer calculated estimates of cost effectiveness for each of the subgroups identified in the decision problem (see table 6). The manufacturer stated that it was not possible to perform an analysis on the stage IVB women as there were too few women in the trial.

Table 6 Deterministic cost-effectiveness results from the MS for the subgroups - direct comparison.

Treatment arm	Mean costs*	Mean QALYs (LYs)*	Incremental cost	Incremental QALYs (LYs)	Cost/QALY (Cost/LYG)
Licensed population excluding stage IVB women					
Topotecan + cisplatin	£6889	0.81 (1.14)	£4938	0.26 (0.31)	**£18,991 (£15,691)**
Cisplatin	£1951	0.55 (0.83)			
Cisplatin-naive population including stage IVB women					
Topotecan + cisplatin	£5522	0.98 (1.30)	£3521	0.32 (0.37)	**£10,928 (£9564)**
Cisplatin	£2001	0.66 (0.93)			
Cisplatin-naive population excluding stage IVB women					
Topotecan + cisplatin	£5923	1.05 (1.39)	£3954	0.46 (0.47)	**£8662 (£8450)**
Cisplatin	£1968	0.59 (0.93)			
SCFI women					
Topotecan + cisplatin	£5855	0.67 (0.98)	£4145	0.13 (0.20)	**£32,463 (£20,757)**
Cisplatin	£1710	0.55 (0.87)			

*All costs and outcomes discounted at 3.5% per annum. LYs = life years, LYG = life-years gained, QALY = quality-adjusted life year, SCFI = sustained cisplatin-free interval

Sensitivity analyses

The manufacturer provided sensitivity analyses (MS page 123) using alternative utility values, alternative assumptions about wastage of topotecan to include all excess topotecan wasted and no excess topotecan wasted (MS page 110) and alternative assumptions about pre-treatment medication to include pre-treatment medication given on day 1 only rather than days 1 to 3. The results of the sensitivity analyses are given in table 7 for the licensed population. Results of sensitivity analyses for the subgroups are given on pages 137 to 140 of the MS.

Table 7 Sensitivity analysis results from the MS for the licensed population - direct comparison (MS page 136).

Treatment arm	Mean costs*	Mean QALYs (LYs)*	Incremental cost	Incremental QALYs (LYs)	Cost/QALY (Cost/LYG)
Base case					
Topotecan + cisplatin	£6074	0.83 (1.12)	£4122	0.23 (0.27)	**£17,974 (£15,091)**
Cisplatin	£1952	0.60 (0.84)			
Literature based breast cancer utilities					
Topotecan + cisplatin	£6074	0.56 (1.12)	£4122	0.17 (0.27)	**£24,440 (£15,091)**
Cisplatin	£1952	0.40 (0.84)			
Minimal wastage					
Topotecan + cisplatin	£5753	0.83 (1.12)	£3782	0.23 (0.27)	**£16,489 (£13,854)**
Cisplatin	£1952	0.60 (0.84)			
Maximum wastage (no vial re-use)					
Topotecan + cisplatin	£6413	0.83 (1.12)	£4461	0.23 (0.27)	**£19,453 (£16,333)**
Cisplatin	£1952	0.60 (0.84)			
Pre-treatment medication on day 1 only					
Topotecan + cisplatin	£5872	0.83 (1.12)	£3921	0.23 (0.27)	**£17,095 (£14,353)**
Cisplatin	£1952	0.60 (0.84)			

*All costs and outcomes discounted at 3.5% per annum. LYs = life years, LYG = life-years gained, QALY = quality-adjusted life year

Indirect comparison

The manufacturer stated that the ICER for topotecan plus cisplatin compared with cisplatin alone was £19,964 per life-year gained (LYG). Paclitaxel plus cisplatin was dominated (that is, it was associated with greater costs and fewer LYGs than topotecan plus cisplatin, see table 8).

Table 8 Cost-effectiveness results for the indirect comparison with paclitaxel in the MS.

	Mean cost per woman	Incremental cost	Mean life years	Incremental life years	ICER: cost per life-years gained
Cisplatin	£2395		0.87		
Topotecan + cisplatin	£7310	£4915	1.12	0.25	**£19,964 (vs. cisplatin)**
Paclitaxel + cisplatin	£7587	£277	0.94	-0.17	**Dominated (by topotecan + cisplatin)**

ICER: incremental cost-effectiveness ratio

Following clarification from the ERG the manufacturer provided a revised model that included utility values to estimate the cost per QALY gained rather than LYG. The model incorporated PFS data from the clinical trial as well as overall survival estimates and used a 36 month time horizon rather than a 24 month time horizon. In addition the manufacturer provided estimates based on the indirect analysis and the direct analysis using GOG-0204. The manufacturer's revised analysis is described on page 67 of the ERG report. The results of the manufacturer's revised analysis are presented in table 9.

Table 9 Results of the indirect cost-effectiveness analysis after clarification (including progression-free survival and utility values).

	Mean cost per patient	Mean QALYs gained	Incremental cost	Incremental QALYs	ICER: cost per QALY gained
GOG-169 indirect analysis – branded Taxol price					
Topotecan + cisplatin	£7310	0.67	-£277	0.12	Topotecan + cisplatin dominated paclitaxel plus cisplatin
Paclitaxel + cisplatin	£7587	0.55			
GOG-169 indirect analysis – 50% of Taxol price					
Topotecan + cisplatin	£7310	0.67	£1450	0.12	£12,213 (topotecan vs paclitaxel)
Paclitaxel + cisplatin	£5860	0.55			
GOG-204 direct analysis – branded Taxol price					
Topotecan + cisplatin	£7310	0.67	£277	0.11	£13,260 (paclitaxel vs topotecan)
Paclitaxel + cisplatin	£7587	0.78			
GOG-204 direct analysis – 50% of Taxol price					
Topotecan + cisplatin	£7310	0.67	-£1450	0.12	Paclitaxel + cisplatin dominated topotecan plus cisplatin
Paclitaxel + cisplatin	£5860	0.55			

QALY: quality-adjusted life year, ICER: incremental cost-effectiveness ratio

3.2 Evidence Review Group comments

The ERG stated that due to a lack of coding for the SAS model a complete validation of the individual patient-level direct comparison was not possible. In addition, the ERG raised concerns about the external validity of the direct comparison model and considered that the indirect comparison model may potentially have greater external validity.

The ERG noted a number of specific issues:

- The health-related quality-of-life (HRQoL) estimates did not appear to have been derived accurately because of incorrect mapping of data utility values (page 52 of the ERG report). The impact of mortality appeared to have

been double counted and there were concerns about the imputation methodology (page 54 of the ERG report).

- The administration costs of topotecan plus cisplatin during the second and third day's administration were potentially under-estimated. In addition, assumptions about wastage of excess topotecan were not fully explored and the costing of adverse events potentially excludes costs of multiple adverse events where these are incurred across separate cycles of treatment.

For these reasons the ERG did not regard the ICERs generated by the direct comparison to be a reliable indication of the cost effectiveness of topotecan.

The ERG noted that the key issues in relation to the indirect comparison were:

- the lack of HRQoL considerations (this was subsequently resolved by the manufacturer in the response to clarification)
- the appropriateness of the metastatic breast cancer utility values adopted in the absence of more suitable cervical carcinoma values
- the reasonableness of the costing assumptions, mainly surrounding the cost of administering topotecan
- the number of vials of topotecan required
- the cost of adverse events
- the exclusion of dose reduction
- the correct source of the hazard ratio used to estimate survival for paclitaxel plus cisplatin (deriving this hazard ratio from GOG-0169 favoured topotecan, but deriving it from GOG-0204 favoured paclitaxel).

In comparing the two economic analyses, the ERG noted a difference in the mean costs obtained from the direct and indirect models. The ERG state that for the direct comparison the mean costs associated with topotecan and cisplatin are £5522 for the cisplatin naive group. However, in the indirect comparison these costs are £7310. The ERG was unable to fully investigate possible differences in the costings, but considered that these may be due to

differences in costing adverse events or the exclusion of dose reduction in the indirect analysis.

3.3 Exploratory analyses undertaken by the ERG

Because the ERG was unable to completely validate the SAS model, the Excel-based analysis formed the basis of the exploratory additional work. The manufacturer argued in the submission that the least potentially biased comparison would be that between the overall ITT population of GOG-0169 and the cisplatin-naive (IND) population of GOG-0179, including persistent patients. However, the ERG performed their exploratory analyses for both the cisplatin-naive and licensed population.

Utility values

The ERG explored the use of alternative utility values in the economic analyses (ERG report page 70). The first analysis (a) included the original Brown (1998) weights adopted by the manufacturer in their sensitivity analysis, including a starting utility of 0.64. The second analysis (b) included a starting utility value of 0.67 derived from the cancer literature submitted by the manufacturer. The third analysis (c) included a starting utility of 0.72 based on FACT-G in the topotecan clinical trial. Analyses (b) and (c) assumed that the starting utility remained constant until disease progressed. In all scenarios the utility values for subsequent health states were derived from the study of breast cancer by Brown (1998). The impact on the ICERs is shown in table 10. The ERG considered that their preferred scenario was (c) and this was adopted in all subsequent analyses.

Table 10 Results of the ERG-revised model following revisions to utility weights.

Cisplatin-naive population							
Treatment	Costs	Utility weights (a)		Utility weights (b)		Utility weights (c)	
		QALYs	ICER	QALYs	ICER	QALYs	ICER
Cisplatin	£2386	0.4749	N/A	0.5019	N/A	0.5428	N/A
Topotecan + cisplatin	£7300	0.669	£25,309	0.6897	£26,156	0.7433	£24,513
Licensed population							
Treatment	Costs	Utility weights (a)		Utility weights (b)		Utility weights (c)	
		QALYs	ICER	QALYs	ICER	QALYs	ICER
Cisplatin	£2196	0.4276	N/A	0.4511	N/A	0.4872	N/A
Topotecan + cisplatin	£6733	0.5087	£55,926	0.5274	£59,406	0.5707	£54,352

QALY: Quality adjusted life years; ICER: Incremental cost effectiveness ratio.

Administration costs

The ERG considered that the administration costs for topotecan may be under estimated in the MS; £277 for the first dose followed by £51 for each subsequent dose in each cycle (ERG report pages 56 and 72). The ERG stated that more appropriate estimates of the administration costs for each treatment could be taken from Health Resources Guide (HRG) codes SB14Z ('Deliver complex chemotherapy, including prolonged infusional treatment at first attendance: Other') and SB15Z ('Deliver subsequent elements of a chemotherapy cycle: Outpatient') given in the NHS Reference Costs 2006/07. The cost of administration of topotecan was therefore £299 for the first dose and £195 for subsequent doses in 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 assumed to be £299 per cycle.

The ICER for topotecan plus cisplatin compared to cisplatin alone increased from £24,513 per QALY gained, using the manufacturer's original

assumptions, to £31,831 per QALY gained in the cisplatin-naive population (and from £54,352 to £68,885 per QALY gained in the main licensed population). Further details are provided on page 73 of the ERG report. The revised administration costs were then included in subsequent explorations.

Number of vials used

The ERG also explored assumptions about wastage of excess vials of topotecan. In the manufacturer's base case it was assumed that some excess topotecan was re-used, with the cost per cycle estimated to be £488.25. The manufacturer also explored scenarios where none and all topotecan was wasted with costs estimated to be £390.60 and £585.90 respectively. The ERG considered that a scenario of maximum wastage was most consistent with the SPC. However, because of the lack of clear guidance on current practice, the ERG explored scenarios using both minimum and maximum wastage. For the minimum wastage scenario the ERG amended the choice of vials to one 4 mg vial (cost £290.62), for the maximum wastage scenario where unused topotecan was immediately discarded, the choice of vials was six 1 mg vials (cost £585.90, see table 11).

Table 11 Estimates of cost effectiveness using revised assumptions of topotecan wastage.

Minimum wastage (vials of topotecan may be re-used over 3-day administration)						
	Cisplatin-naive population			Licensed population		
Treatment	Costs	QALYs	ICER	Costs	QALYs	ICER
Cisplatin	£2344	0.5428	N/A	£258	0.4872	N/A
Topotecan + cisplatin	£7711	0.7433	£26,778	£7,073	0.5707	£58,872
Maximum wastage (vials of topotecan disposed of immediately following use)						
	Cisplatin-naive population			Licensed population		
Treatment	Costs	QALYs	ICER	Costs	QALYs	ICER
Cisplatin	£2344	0.5428	N/A	£2158	0.4872	N/A
Topotecan + cisplatin	£9224	0.7433	£34,327	£8322	0.5707	£73,833

QALY: Quality adjusted life years; ICER: Incremental cost effectiveness ratio.

Costs associated with dose reduction

The ERG explored the impact of dose reduction (ERG report page 75). The ERG considered that this exploration was limited because it was unable to validate the patient-level SAS analysis from which the baseline costs were derived. However, the analyses demonstrated that incorporating assumptions about dose reduction could have a significant impact on the ICERs. With minimum wastage the ICER for topotecan plus cisplatin compared to cisplatin alone was £19,815 per QALY gained and £53,868 per QALY gained for the cisplatin-naive and licensed populations, respectively. Assuming maximum wastage the ICER for topotecan plus cisplatin compared to cisplatin alone was £27,362 per QALY gained and £68,826 per QALY gained for the cisplatin-naive and licensed population respectively.

Analyses including paclitaxel and cisplatin

The ERG explored including topotecan plus cisplatin, paclitaxel plus cisplatin and cisplatin alone in a fully incremental analysis (ERG report page 77 and

tables 12 and 13 below). This analysis included the revised assumptions about utilities and costs, but not those about dose reduction.

Table 12 Minimum wastage scenario (vials of topotecan disposed of immediately following use).

GOG-0169 hazard ratio employed						
	Cisplatin-naive population			Licensed population		
Treatment	Costs	QALYs	ICER	Costs	QALYs	ICER
Cisplatin	£2344	0.5428	N/A	£2158	0.4872	N/A
Paclitaxel + cisplatin	£7694	0.6107	ED	£6638	0.5562	ED
Topotecan + cisplatin	£7711	0.7433	£26,778	£7073	0.5707	£58,872
GOG-0204 hazard ratio employed						
	Cisplatin-naive population			Licensed population		
Treatment	Costs	QALYs	ICER	Costs	QALYs	ICER
Cisplatin	£2344	0.5428	N/A	£2158	0.4872	N/A
Paclitaxel + cisplatin	£7694	0.8572	£17,021	£6638	0.6915	£21,926
Topotecan + cisplatin	£7711	0.7433	D	£7073	0.5707	D

QALY: Quality adjusted life years; ICER: Incremental cost effectiveness ratio.

Table 13 Maximum wastage scenario (vials of topotecan disposed of immediately following use).

GOG-0169 hazard ratio employed						
	Cisplatin-naive population			Licensed population		
Treatment	Costs	QALYs	ICER	Costs	QALYs	ICER
Cisplatin	£2344	0.5428	N/A	£2158	0.4872	N/A
Paclitaxel + cisplatin	£7694	0.6107	ED	£6638	0.5562	£64,865
Topotecan + cisplatin	£9224	0.7433	£34,327	£8322	0.5707	£116,788
GOG-0204 hazard ratio employed						
	Cisplatin-naive population			Licensed population		
Treatment	Costs	QALYs	ICER	Costs	QALYs	ICER
Cisplatin	£2344	0.5428	N/A	£2158	0.4872	N/A
Paclitaxel + cisplatin	£7694	0.8572	£17,021	£6638	0.6915	£21,926
Topotecan + cisplatin	£9224	0.7433	D	£8322	0.5707	D

QALY: Quality adjusted life years; ICER: Incremental cost effectiveness ratio.

D = dominated

ED = extendly dominated

4 Authors

Andres Roman (Technical Lead) and Zoe Garrett (Technical Adviser) with input from the Lead Team (Ann Richardson, William Turner, Simon Dixon).

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

The evidence review group (ERG) report for this appraisal was prepared by Centre for Reviews and Dissemination (CRD), Centre for Health Economics (CHE):

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):

- Paton F, Paulden M, Saramago P et al. Topotecan for the treatment of recurrent and stage IVB carcinoma of the cervix: A single technology appraisal. Centre for Reviews and Dissemination, Centre for Health Economics, University of York, April 2009.

B Submissions or statements from the following organisations:

I Manufacturer/sponsor

- GlaxoSmithKline

II Professional/specialist, patient/carer and other groups:

- Rarer Cancers Forum
- Royal College of Nursing
- Royal College of Pathologists