All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

AWMSG ADVICE SUPERSEDED BY NICE GUIDANCE (TA183)

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Final Appraisal Report

Intravenous topotecan (Hycamtin®)

GlaxoSmithKline UK Ltd.

Advice No: 0208 – February 2008

Recommendation of AWMSG

Intravenous topotecan (Hycamtin®) is recommended for use within NHS Wales in combination with cisplatin, for the treatment of patients with carcinoma of the cervix recurrent after radiotherapy and for patients with Stage IVB disease. It is restricted for use in patients who are cisplatin-naïve.

Topotecan (Hycamtin®) should only be initiated by specialists experienced in the treatment of cervical cancer.

Topotecan (Hycamtin®) is not presently recommended for shared care.

This report should be cited as:

All Wales Medicines Strategy Group Final Appraisal Report
Topotecan (Hycamtin®) for cervical carcinoma
February 2008

1.0 RECOMMENDATION OF AWMSG:

Date: 14th February 2008

The recommendation of AWMSG is:

Intravenous topotecan (Hycamtin®) is recommended for use within NHS Wales in combination with cisplatin, for the treatment of patients with carcinoma of the cervix recurrent after radiotherapy and for patients with Stage IVB disease. It is restricted for use in patients who are cisplatin-naïve.

Topotecan (Hycamtin®) should only be initiated by specialists experienced in the treatment of cervical cancer.

Topotecan (Hycamtin®) is not presently recommended for shared care.

Key factors influencing the recommendation:

- Overall and progression-free survival was longer for cisplatin plus topotecan compared with cisplatin alone, particularly where cisplatin had not previously been used.

- The topotecan and cisplatin combination is judged as cost effective compared to cisplatin alone for women who are cisplatin naïve, but not for those who have had a sustained cisplatin-free interval.

Additional note:

More patients in the cisplatin and topotecan group received supportive haematological therapy due to adverse effects compared with the cisplatin only group.

2.0 PRODUCT DETAILS:

2.1 Licensed indication:
Topotecan (Hycamtin®), 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[1].

2.2 Dosing:
The recommended dosage of topotecan is 0.75 mg/m^2/day administered as a 30 minute intravenous infusion daily on days one, two and three. Cisplatin is administered as an intravenous infusion on day one at a dose of 50 mg/m^2/day and following the topotecan dose. This treatment schedule is repeated every 21 days for six courses or until progressive disease[1].

2.3 Market authorisation date: 22nd November 2006[2]

2.4 UK Launch date: 22nd November 2006

3.0 DECISION CONTEXT
This appraisal focuses on topotecan treatment for cervical cancer. Topotecan is also licensed for ovarian cancer and small cell lung carcinoma (SCLC). NICE has issued guidance on topotecan for the second line treatment of ovarian cancer[3]. SCLC is the subject of AWMSG appraisal number 0108.

Cervical cancer is the second most common cancer in women worldwide and in countries with efficient screening, advanced disease is relatively rare. Overall there are about 38,000 new cases of cervical cancer a year within the European Union (EU) and about 17,000 associated deaths[4]. In the EU, most patients are diagnosed with early disease and surgery is curative. In more advanced non-metastatic disease radiochemotherapy is administered with curative intent. In cases of persistent, recurrent or metastatic disease, treatment is in most cases administered with palliative intent[4]. Stage IVB cervical cancer is the most advanced form which has usually spread further than the pelvic region to more distant organs such as the lungs[4]. According to the company submission, the objectives of treatment are to improve overall survival (OS) and progression-free survival (PFS) whilst maintaining an acceptable toxicity profile and maintaining or improving patient quality of life (QOL)[5].

The company submission states that approximately 30 patients per year in Wales develop cervical cancer that is either recurrent after radiotherapy or metastatic (stage IVB) and are therefore eligible for chemotherapy. Treatment options are limited for these patients, hence they are currently treated with single agent cisplatin, but also with unlicensed regimens which have not been fully investigated in advanced cervical cancer, such as carboplatin with or without paclitaxel and bleomycin with mitomycin-C and cisplatin (BMC)[5].

Topotecan is a cytotoxic agent; a semi synthetic analogue of the alkaloid camptothecin. It exerts its activity by the inhibition of the nuclear enzyme topoisomerase I that is involved in DNA replication[1].

4.0 EXECUTIVE SUMMARY:

4.1 Review of the evidence on clinical effectiveness

The company have based their submission on one randomised, comparative study of topotecan plus cisplatin, versus cisplatin alone, in the treatment of stage IVB or recurrent cervical cancer. A phase II study is mentioned within the submission as supporting data only.

Topotecan as add-on therapy to a standard cisplatin regimen versus cisplatin alone has been demonstrated to result in a borderline significant (p=0.03) prolongation of overall survival (Hazard Ratio (HR) 0.76, median survival 9.4 and 6.5 months, respectively).The median time until disease progression was lengthened in the combination group: 4.6 months compared to 2.9 months in the cisplatin-only group. There was a greater benefit from topotecan and cisplatin in patients who had not received prior exposure to cisplatin therapy. This is reflected in the licence which requires a treatment-free interval for those patients with prior cisplatin use.

The GOG-0179 study population, however, was heterogeneous and not considered to be fully representative of current clinical practice.

Patients who received combination treatment experienced more haematological adverse effects and a higher infection rate than those on cisplatin alone. Quality of life data rated the patient experience as moderate and very similar for both treatment groups. These factors suggest that the benefits and risks to the whole drug population require careful consideration.

4.2 Review of the evidence on cost-effectiveness

The company submitted two economic analyses: a primary analysis based on trial data that assessed the cost-effectiveness of topotecan plus cisplatin against cisplatin monotherapy, and a secondary "indirect" analysis which modelled the cost-effectiveness of topotecan plus cisplatin versus paclitaxel plus cisplatin.

The primary analysis used survival data derived from a phase III trial weighted by proxy utility values estimated by nurses for patients with breast cancer, rather than cervical cancer. There are some issues with the application of these utility values and, in particular, how they relate to the haematological adverse effects of topotecan plus cisplatin, which introduces a degree of uncertainty. The base case analysis for the whole licensed indication, and the subgroup of cisplatin-naïve patients, indicates that the incremental cost per QALY may fall below conventional thresholds of cost-effectiveness. However, for the subgroup of the licensed population who are cisplatin-experienced, the incremental cost per QALY exceeds £30,000.

In the secondary "indirect" analysis (which was based on an analysis that included patients not meeting the licensed indication for topotecan), paclitaxel plus cisplatin was dominated by topotecan plus cisplatin on the basis of higher costs and lower effectiveness (incremental costs over topotecan plus cisplatin were £285 and mean life years were lower by 0.17).

The comparators included in both analyses, however, do not represent the medicines that are most likely to be displaced by the introduction of topotecan for its licensed indication in Wales. According to data obtained by the company on the most frequently prescribed regimens for patients with recurrent and stage IVB cervical cancer in Wales, cisplatin monotherapy is used only in a small minority of patients

(approximately 7.5%). Paclitaxel plus cisplatin is not reported to be used at all. Therefore the analyses cannot be regarded as wholly appropriate for addressing the decision problem.

5.0 LIMITATIONS OF DECISION CONTEXT:

- Cisplatin monotherapy, which is the comparator studied, is not representative of the regime which would be replaced by the introduction of topotecan for its licensed indication in Wales. Regimens currently used are not supported by comparative studies and it is therefore difficult to make a robust comparison with topotecan and cisplatin[5].

- A cost analysis of other chemotherapy regimens used in Wales is presented within the company submission. However, as there is a lack of robust evidence of superiority of these regimens over cisplatin, analysis needs to be treated with extreme caution as, in effect, it represents a cost-minimisation analysis without supporting evidence on therapeutic equivalence.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

6.1 Clinical efficacy:

The company submission describes two studies of topotecan plus cisplatin in the treatment of stage IVB or recurrent cervical cancer; a pivotal randomised phase III study and a supportive phase II single arm trial for which no detail is submitted[5].

6.1.1 Study GOG - 0179: Pivotal Randomised Phase III trial of cisplatin with or without topotecan in cervical cancer: a Gynaecological Oncology Group (GOG) study [5,6].

This was a randomised phase III study originally with three arms:

- topotecan 0.75mg/m^2 intravenously on days one to three every three weeks plus cisplatin 50mg/m^2 intravenously on day one repeated every three weeks (n=147)

- cisplatin 50mg/m^2 intravenously on day one every three weeks (n=146)

- methotrexate/vinblastine/doxorubicin/cisplatin (MVAC) (n=63)

The MVAC arm was closed to patient entry due to excess toxicity before the study finished and, unfortunately, results are not published within the analysis[5].

All enrolled patients had advanced, recurrent or persistent carcinoma of the cervix and were unsuitable for surgery and/or radiotherapy. The majority of patients were Caucasian, aged less than 65 years of age at study entry, had squamous cell carcinoma and a performance status (PS) of 0 or 1 (Appendix I, table 1). Treatment duration was for six cycles (21 day cycles) or until disease progression or toxicity prevented continuation of treatment[5].

The primary objective of this study was improvement of OS (all cause mortality), which was defined as the time from randomisation until death in the intent-to-treat (ITT) population, or until date of last contact for patients still alive at this point[5].

The secondary objectives of the study were to compare the three treatment regimes for:

- progression-free survival (PFS), defined as the minimum amount of time from randomisation until clinical progression, death or date of last contact.
- response rates (RR) (see Appendix 1)
- toxicities (see section 6.1)
- health related quality of life (HRQoL) (see Appendix 1)

The final efficacy analysis was performed after 129 events (deaths) had occurred in the cisplatin group. The efficacy data base was locked on 31st October 2003 and these data were used for the trial efficacy analyses[5].

Additional sub-group analyses were undertaken for this submission, as the licence for topotecan plus cisplatin does not include all patients in the GOG-0179 trial. The "*licenced population*" excludes patients with persistent disease (32 patients, 11% of the ITT population) and those patients without a sustained cisplatin-free interval (SCFI) (39 patients, 13% of the ITT population). The SCFI is assumed as 180 days within this submission, which relates to the period between the last cisplatin dose and disease recurrence[5]. As there is uncertainty as to the extent of cisplatin exposure within Wales, the company have also analysed the two sub groups within the "*licenced population*":

- Cisplatin naïve population (both advanced and recurrent disease patients)
- SCFI population

A further sub-group of cisplatin naïve patients was analysed specifically for an indirect cost-effectiveness comparison of topotecan plus cisplatin versus paclitaxel and cisplatin (study GOG-0169), this is discussed in Appendix 2. The number of cisplatin naïve patients within this sub group is slightly higher than that compared here as it includes eight cisplatin naïve patients with persistent disease[5].

Results for ITT population

Response is defined in accordance with the GOG criteria, as the study was activated before adoption of the Response Evaluation Criteria in Solid Tumours Group. Table 1 illustrates the borderline significant (p=0.03) prolongation of overall survival as the primary outcome measure in the ITT population of GOG-0179[5,6].

Table 1 Overall Survival (ITT population) [5,6]

Overall survival time (months)	Cisplatin (n=146)	Topotecan plus Cisplatin (n=147)
Median	6.5	9.4
95% CI for median survival time	5.8-8.8	7.9-11.9
Log-rank p-value	0.033[a]	
Hazard ratio (95% CI)[b]	0.762 (0.593 to 0.979)	
Minimum	0.3	0.2
Maximum	39.0	34.4
Observed Events	129 (88.4%)	118 (80.3%)
Censored Events	17 (11.6%)	29 (19.7%)

[a] Log-rank p-value was significant (< 0.044 adjusted significance level)
[b] After adjusting for covariates of age, performance status and disease status at study entry, the hazard ratio was 0.76 (95% CI:0.59 to 0.98; p=0.033) favouring the combination arm.

The Kaplan Meier plot (Appendix 1, figure 1) illustrates a separation of the survival curve from approximately four months. Thirty-six months after the start of the trial, 129 patients in the cisplatin-only group and 118 patients in the combination group had died[5,6].

PFS as a secondary outcome measure, illustrates a 24% decrease in event rate for the combination therapy compared to cisplatin alone as detailed in Table 2:

Table 2 Progression-free survival (ITT population)[5,6]

Total population	Progression-free survival time (months)	
	Cisplatin *n=146*	**Topotecan plus Cisplatin *n=147***
Median	2.9	4.6
95% CI for median survival time	2.6 to 3.5	3.5 to 5.7
Log-rank p-value	p = 0.026	

Response rate within the ITT population was higher for the combination treatment (36/147; 24%) compared to cisplatin alone (18/146;12%) (p=0.0073). The median time until disease progression was lengthened in the combination group: 4.6 months compared to 2.9 months in the cisplatin-only group[5,6].

A total of 145 patients in each treatment group were included in the QoL analysis. Despite differences in the tolerability profile between the two treatment groups (see section 6.1), mean HRQoL scores were similar for both groups in this open label study[6].

Results for sub-group populations
The topotecan plus cisplatin arm of the cisplatin naïve population had a median OS of 14.5 months compared to 8.5 months for cisplatin (HR 0.587, 95% CI: 0.389 to 0.884). This is the highest of any of the subgroups.

The topotecan plus cisplatin arm in the SCFI population had a median OS of 9.9 months (versus 6.3 months for cisplatin, HR 0.75, 95% CI: 0.492 to 1.155), the lowest of any subgroup (although not statistically significant). This suggests that patients who have received prior treatment with cisplatin do not respond as well as those with no prior cisplatin therapy. In addition the added value of topotecan is smaller for these patients[4].

In the sub-group analysis, the topotecan and cisplatin arm of the SCFI population had fewer patients (21/49; 43%) with a PS of 0 compared to the same arm of the cisplatin-naïve population (35/58; 60%)[5,6].

Points to note

- 60% of patients were previously treated with cisplatin containing chemo-radiotherapy. This is probably reflective of the standard treatment while the study was conducted between 1999 and 2002. Nowadays chemoradiotherapy is considered standard[4].

- The European Medicines Agency (EMEA) state that the treatment effect in terms of overall survival is of borderline statistical significance and has to be scrutinised as regards consistency in relation to reasonably defined treatment subgroups and in relation to secondary endpoints and safety[4].

- A low number of patients (n=32) with persistent disease were enrolled in the trial, and this is reflected in the licensed indication which is for recurrent disease post radiotherapy and stage IV only[6].

- No appreciable differences were observed between the treatment arms with respect to the use of post study (salvage) therapy. Approximately 44% of topotecan/cisplatin and 42% of cisplatin patients received at least one post-study chemotherapy regimen[4].

- 31% of patients in the topotecan-cisplatin arm and 24% of patients in the cisplatin arm were withdrawn from study therapy for reasons other than progression or death[4].

- Sub group analysis does seem appropriate, but it should be noted that these were *post hoc* analyses and the power of the study to detect true differences in effect between the treatment regimens in the sub groups is reduced.

- In consideration of the difference in performance status (PS) between the topotecan and cisplatin arms within the sub-group analysis, there is a possibility of increased benefit with a better performance status, hence a potential resulting impact on the results within the cisplatin naïve population.

- Sub-group analysis shows that previous cisplatin therapy appears to increase the likelihood of resistance to subsequent chemotherapy whether it is cisplatin monotherapy or the combination of cisplatin and topotecan[4].

- Topotecan is administered intravenously over three days[1], therefore requiring three hospital visits per cycle compared to one for other regimens.

6.1.2 Study GSK-CRT-234: Topotecan plus cisplatin in persistent or recurrent squamous and non-squamous carcinomas of the cervix[7].
This was a phase II single arm study designed to test the safety and efficacy of a topotecan plus cisplatin combination in patients with persistent or recurrent squamous cell or non-squamous cell cervical cancer. It generated data to support the licence application and on which the design of study GOG-0179 was based[7].

35 patients were enrolled within this study, 32 were evaluated. Exclusion criteria included prior chemotherapy and 94% of patients had received prior radiation therapy. The same regimen of cisplatin and topotecan as in the pivotal study was investigated and the median number of courses administered was five (range 1-10).

The overall response rate was 28% (9/32); three complete and four partial responses. The median overall survival was 10 months (range 1 to 41+) and the median duration of response was five months (range 2 to 18+). The median progression-free survival (PFS) was 5 months (range 1 to 41+). The regimen was considered tolerable[4,5].

6.2 Safety:
140 patients were exposed to the cisplatin-topotecan combination within the GOG-0179 study. The median number of cisplatin-topotecan cycles administered was four (range 1 to 20) and 567/628 of the cycles were administered at the protocol defined starting dose[4,5].

The most frequently reported additional adverse events for the combination cisplatin-topotecan compared with cisplatin monotherapy were events related to myelosuppression.

Appendix 1, table 2, details haematological toxicity differences between the treatment arms within GOG-0179. The incidence of febrile neutropenia was not directly measured, but classified as a subset of the infection category. 15 patients had dosage reductions within the topotecan and cisplatin treatment group due to febrile neutropenia. The incidence of grade 3 and 4 neutropenia and leucopoenia was substantially higher in the combination arm. The incidence of thrombocytopenia was much higher within the combination arm: 45% for grade 1/2 and 34% for grade 3/4 compared to cisplatin alone with 10% and 4% incidence, respectively. It should be noted that the company submission states that "the incidence of severe thrombocytopenia was low in both treatment groups"[5], which does not appear to be consistent with the figures reported. Overall, the haematological toxicities with topotecan plus cisplatin treatment were well managed with dose delays and/or dose reductions and did not lead to increased serious adverse effects (SAEs), withdrawals, deaths or a reduction in HRQoL when compared to the cisplatin treatment group[5].

Three patients (2%) treated with cisplatin and two patients (1%) on combination therapy were withdrawn due to SAEs[6].

In general, the incidence of non-haematological toxicities between the two treatment groups was comparable. The most significant difference in non haematological toxicity within the treatment arms was that of grade 2 dermatological adverse events; 47% for the combination group and 20% for the cisplatin monotherapy group[5].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES:

7.1 Comparator medications:

Several different chemotherapy regimens are employed in the treatment of cancer of the cervix, although some are not specifically licensed for cervical cancer[8]. Cisplatin is used as the main agent for recurrent and stage IVB cervical cancer in many areas. In Wales, it is used alongside a variety of regimens; carboplatin, carboplatin/paclitaxel and bleomycin/mitomycin C/cisplatin (BMC)[5] some of which are unlicensed.

7.2 Comparative effectiveness:

Most of the combination regimes used alongside cisplatin are not supported by phase III comparative studies for treatment of recurrent cervical cancer, making it very difficult for a robust comparison with topotecan and cisplatin. An indirect sub group analysis of topotecan and cisplatin treated cisplatin naïve patients is compared to paclitaxel and cisplatin treated patients from GOG-0169 for cost-effectiveness purposes only within this submission (see Appendix 2)[5].

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE:

8.1 Overview of the key economic issues for the AWMSG to consider

The key economic issue for the AWMSG to consider is whether any additional benefits offered by the use of topotecan plus cisplatin over relevant comparators justify any associated increase in costs.

8.2 Review of published evidence on cost-effectiveness

Standard searches conducted by the Welsh Medicines Partnership (WMP) have not identified any other published economic studies of the use of topotecan in the treatment of cervical cancer.

8.3 Review of the company submission on cost-effectiveness

8.3.1 Summary of the evidence

The primary cost-utility analysis compares topotecan plus cisplatin versus cisplatin alone[5] .The secondary “indirect” analysis models the cost-effectiveness of topotecan plus cisplatin versus paclitaxel plus cisplatin.

Importantly, the prescribing patterns of clinical experts indicate that cisplatin monotherapy is used to treat only 7.5% of patients in Wales; the combination of paclitaxel plus cisplatin does not appear to be used at all. The company analysis does not provide evidence of cost-effectiveness against the regimens used in Wales, and therefore cannot be regarded as wholly appropriate for addressing the decision problem.

The primary analysis presented uses patient-level data from a phase III trial of topotecan and cisplatin (GOG-0179) that was re-analysed for those subjects in the trial that meet the licensed indication and its sub groups (cisplatin-naïve patients and those previously exposed to cisplatin 180 days or more before recurrence of disease [sustained cisplatin-free interval, SCFI]). These approaches would seem appropriate but it should be noted that these were *post hoc* analyses.

The base-case analysis uses published proxy estimates of utility values made by nurses in relation to metastatic breast cancer to weight the trial-derived survival estimates[6]. There are obvious limitations to this approach, but in addition to these, the utility values taken from the published breast cancer study have been inconsistently applied such that the impact of the adverse events that occur more commonly with topotecan plus cisplatin than with cisplatin alone (febrile neutropenia and thrombocytopenia) is underestimated. This would bias the analysis in favour of topotecan. Non-haematological adverse events were not considered to have an impact on utility values, but serious treatment-related adverse events have been costed. Trial-derived utility values were explored in a sensitivity analysis.

Chemotherapy regimens are costed on the basis of patient-level data with the exception of mean body surface area (assumed to be $1.7m^2$, as used in recent NICE technology appraisals in ovarian cancer and breast cancer)[5]. Other costs in the analysis include hydration treatment for use with cisplatin, pre- and post-treatment antiemetic medication and steroid, the costs of pharmacy, nurse and day case attendance/outpatient visits, and follow-up costs. The impact of wastage from vials is explored in sensitivity analyses.

A secondary "indirect" cost-effectiveness analysis compares data from trial GOG-0179 with that obtained from a trial of paclitaxel plus cisplatin versus cisplatin alone (GOG-0169) [5,7]. Data from the whole intention to treat population of trial GOG-0169 (including patients not meeting the licensed indication for topotecan) were compared with cisplatin-naïve patient data from GOG-0179 (including a small number of patients with persistent cervical cancer outside the licensed indication for topotecan). No utility values were applied to the survival data from GOG-0169. Therefore, the modelled cost-effectiveness refers to the incremental cost per life-year gained for topotecan plus cisplatin versus paclitaxel plus cisplatin (which is a relatively expensive and apparently uncommonly used regimen in Wales)[5] , in a sub group of patients who may not fully meet the licensed indication for topotecan. Therefore, there are several issues which limit the usefulness of this analysis.

8.3.2 Summary of the key findings

In the whole licensed population, the base-case analysis indicates a cost per Quality Adjusted Life Year (QALY) gained of £24,115 for topotecan plus cisplatin versus cisplatin alone. In the cisplatin-naïve sub group, the Incremental Cost Effectiveness Ratio (ICER) reduces to £15,543 per QALY gained. However, in the cisplatin-experienced SCFI subgroup, the ICER increases to £34,076 per QALY gained, primarily due to reduced QALY gains[5].

In the one-way sensitivity analyses, the use of trial-derived utility values instead of the literature-based breast cancer treatment utility values reduced the ICER in all groups but less so in the SCFI population (licensed population ICER £17,736 per QALY gained)[5]. In the Probalistic Sensitivity Analysis (PSA), the bootstrap mean ICER was higher for the licensed population but lower for the sub groups compared with the base-case analysis results (licensed population £25,939 per QALY gained). The probabilities of topotecan plus cisplatin being cost-effective at a threshold of £20,000 and £30,000 per QALY gained were 0.27 and 0.61 in the whole licensed population, 0.74 and 0.90 in the cisplatin-naive population, and 0.21 and 0.54 in the SCFI population, respectively, when using the breast cancer utility values. Using the trial-derived utility values increased all of these probabilities. As patients were not blinded to therapy, there is a potential for bias, and favourable reporting of health outcomes.

In the secondary "indirect" analysis, paclitaxel plus cisplatin was dominated by topotecan plus cisplatin on the basis of higher costs and lower effectiveness (incremental costs over topotecan plus cisplatin were £285 and mean life years were lower by 0.17). For topotecan plus cisplatin versus cisplatin alone, the incremental cost per life year gained was £19,768 over a 24 month time horizon[5].

Given the issues discussed in relation to the comparators, the ICERs presented in the company submission are of questionable relevance to the decision problem.

8.4 Review of evidence on budget impact:

8.4.1 Summary of the evidence

The perspective adopted by the budget impact analysis is that of NHS Wales, with a five-year time horizon[5]. The company submission states that there would be around 30 patients meeting the licensed indication for topotecan in Wales each year. This has been estimated by working backwards from the number of deaths in Wales from 2005 (73 deaths). It is assumed that the proportion of women with persistent cancer in Wales would be the same as in the population of trial GOG-0179 (11%), which would mean that 89% (65 patients) would have recurrent and stage IVB cancer. 75% of these patients have been estimated to be eligible for chemotherapy, based on expert opinion (equivalent to 49 patients). Of these, 60% (30 patients) have been estimated to be either cisplatin-naïve or to have had a SCFI, again based on expert opinion[5].

Based on the treatment regimens used by three oncologists in Wales who, it is stated, treat nearly all of the relevant patients, cisplatin alone is used in 7.5% of patients, BMC in 42.5%, carboplatin in 33.3% and carboplatin plus paclitaxel in 16.7%. The company submission assumes that topotecan would be adopted in 40% of eligible patients in year 1, rising to 80% in year 5, with replacement of the current chemotherapy regimens in equal proportions[5].

8.4.2 Summary of the key findings

Based on reported current prescribing patterns across the whole of Wales, the uptake of topotecan in year 1 (40%) would increase costs by £26,684, rising to £53,369 in year 5 (80%). Based on current prescribing of cisplatin regimens only (15% cisplatin alone or 85% BMC, as used by one of the Welsh oncologists) in half of all eligible patients (i.e. 15 patients), the uptake of topotecan in year 1 (40%) would increase costs by £17,910, rising to £35,820 in year 5 (80%)[5]. Based on current prescribing of carboplatin regimens only (67% carboplatin alone or 33% paclitaxel plus carboplatin, as used by one of the Welsh oncologists) in half of all eligible patients (i.e. 15 patients), the uptake of topotecan in year 1 (40%) would increase costs by £8,775, rising to £17,549 in year 5 (80%)[5].

9.0 ADDITIONAL INFORMATION:

9.1 Guidance and audit requirements:

- Topotecan would not be suitable for a shared-care agreement. Treatment initiation, monitoring and supervision should be retained under Specialist care.
- UK guidance on the treatment of cervical cancer is currently not available.

9.2 Previous AWMSG/NICE advice:

Guidance on the use of liquid based cytology for cervical screening was published by NICE in 2003 (Technology Appraisal Guidance (TAG) 69). There is no current recommendation on THE treatment of cervical cancer from NICE or AWMSG[9].

9.3 Ongoing studies

- GOG-0204. A phase III trial of topotecan and cisplatin in recurrent advanced and persistent cervical cancer versus paclitaxel and cisplatin, vinorelbine and cisplatin and gemcitabine and cisplatin has enrolled 500 patients[10]. Results are expected in the second quarter of 2008.

- Protocol 106415. A study for recurrent and persistent cervical cancer treated with topotecan and cisplatin versus topotecan and paclitaxel has enrolled 326 patients. Results are expected in 2010[5].

9.4 Medical expert summary

Medical expert opinion was sought prior to the meeting as summarised below, and provided to NMG members:

The medical expert opinion received stated that recurrent cervical cancer is not a common condition, but treatment remains poor with palliative chemotherapy being the mainstay of therapy. There is a need for better and less toxic regimens as some patients may not be fit enough to receive cisplatin-based chemotherapy. Members were informed that a range of chemotherapy regimens are used but all will contain cisplatin usually in combination with other drugs. The aim of combination therapy is to increase the response rate and hence make the treatment more effective. However, combination therapy also increases the toxicity of treatment. Cisplatin may therefore sometimes be used as a single agent. The medical expert view was that there is a scarcity of data to guide the choice of regimen and the regimen that gives the best balance of effectiveness and toxicity is not known. Therefore there is a wide variation in choice of cisplatin-containing regimens used within this setting. The medical expert view was that the preferred current treatment option is cisplatin in combination with bleomycin and mitomycin-C. If topotecan were available then an interest was expressed to use it in combination with cisplatin instead of other cisplatin-containing combinations.

9.5 Patient interest group

A patient interest group submission was received from Jo's Trust Fighting Cervical Cancer.

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APPENDIX 1. Additional Clinical Information

Table 1: Explanation of Gynaecological Oncology Group (GOG) performance status[5]:

GOG Score	ECOG Score	Karnofsky Score	Activity Level
0	0	90-100	Fully active, unrestricted activities of daily living
1	1	70-80	Ambulatory, but restricted in strenuous activity
2	2	50-60	Ambulatory, and capable of self care. Unable to work. Out of bed for greater than 50% of waking hours

The following definitions were used[5]:

RR: The percentage of all eligible patients responding to treatment; i.e. patients with complete response (CR) or partial response (PR) divided by the total number of patients in each group in the ITT population

Complete response (CR): Complete disappearance of all gross evidence of cancer for at least four weeks

Partial response (PR): At least a 50% decrease in the cross-product dimensions of each tumour compared to the cross-product dimensions reported on the first cycle of therapy for at least four weeks

Progressive disease (PD)*: At least 50% increase in the cross-product dimensions of any tumour compared to the cross-product dimensions reported on the first cycle of therapy and occurring within eight weeks of study entry or the appearance of any new lesion within eight weeks of study entry

* The GOG definition of PD used in GOG-0179 differs slightly from that of the WHO criteria, i.e. GOG criteria is a 50% or greater increase in the cross-product from any lesion or a new lesion, compared to the WHO criteria, a 25% or greater increase in the cross-product from any lesion or a new lesion (WHO criteria).

Health-related quality of life (HRQoL) was measured prospectively and was assessed with the following instruments[5]

- The Functional Assessment of Cancer Therapy: Cervix cancer (FACT-Cx): The FACT-Cx is the Functional Assessment of Cancer Therapy – General (FACT-G) plus a cervix cancer-specific subscale. The FACT-G is a 27-item self-reporting QoL measure developed and validated among cancer patients for use in clinical trials. It includes four subscales (physical well-being, functional well-being, social well-being, and emotional well-being). Each scale produces a separate score that can be summed into one total QoL score. The cervix subscale of the FACT consists of 15 items developed by cervical cancer patients and clinicians. Along with the cervix subscale, six items measuring neurotoxicity (NTX) were included to take into account the side effects that may result from the variable doses of cisplatin.

- The Brief Pain Inventory (BPI)
  The BPI consists of 14 questions designed to assess pain related to cancer and other diseases.

- The UNISCALE
  A single item visual analogue scale that asks the patient to place an “x” on a 0 to 100 mm scale corresponding to overall QoL.

All enrolled patients were expected to complete QoL assessments at four time points (at baseline, just before the second and fifth chemotherapy cycles, and nine months after randomisation) using FACT-G, FACT-Cx, NTX, Brief Pain Inventory and UNISCALE. Treatment effect on QoL before and after chemotherapy was examined, adjusting for patient age, baseline scores and effects of time. Mean QoL scores over time were summarised by treatment group using descriptive statistics. Missing data were tabulated over time by treatment group and by reason.

Figure 1: Kaplan Meier Plot of Survival by Treatment, ITT Population[5]

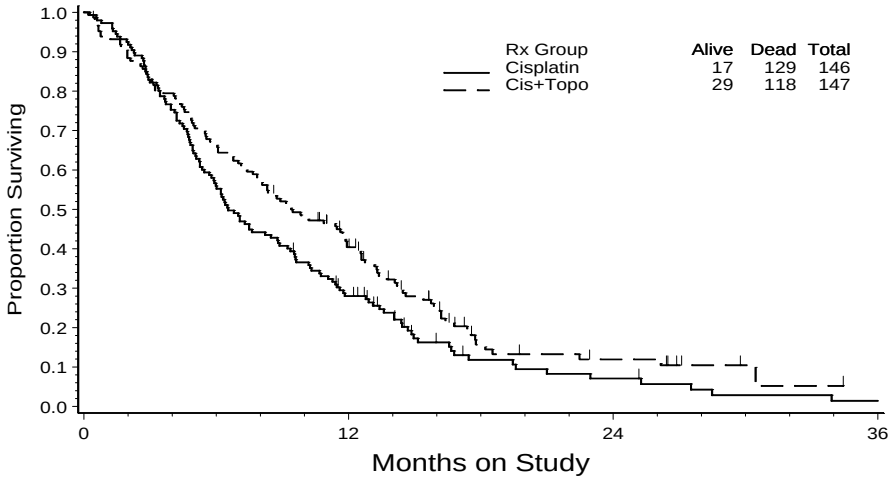

Table 2: Number (%) of patients with haematological toxicity – ITT population[5]

Haematological toxicity	Cisplatin		Topotecan plus cisplatin	
	n	(%)	n	(%)
Leucopenia				
No. patients with lab values	140		137	
Grade 1 / 2	41	(30)	34	(25)
Grade 3 / 4	2	(1)	95	(69)
Neutropenia				
No. patients with lab values	139		133	
Grade 1 / 2	23	(16)	22	(17)
Grade 3 / 4	3	(2)	103	(78)
Thrombocytopenia				
No. patients with lab values	139		135	
Grade 1 / 2	14	(10)	61	(45)
Grade 3 / 4	5	(4)	46	(34)
Haemoglobin				
No. patients with lab values	144		137	
Grade 1 / 2	103	(62)	75	(55)
Grade 3 / 4	34	(24)	59	(43)

APPENDIX 2. Health Economic Review

Company submission - economic evidence

1. Description and critique of the company submission

The company submission describes a primary cost-utility analysis of topotecan plus cisplatin versus cisplatin alone. A secondary "indirect" cost-effectiveness analysis of topotecan plus cisplatin versus paclitaxel plus cisplatin is also presented[5].

The comparators included in the economic analyses do not represent the medicines that are most likely to be displaced by the introduction of topotecan for the licensed indication in Wales. According to data obtained by the company on the most frequently prescribed regimens for patients with recurrent and stage IVB cervical cancer in Wales, cisplatin monotherapy is used only in a minority of cases (approximately 7.5%). Paclitaxel plus cisplatin is not reported to be used at all. Therefore the analyses are severely restricted in terms of their relevance to the Welsh setting.

The primary cost-utility analysis uses patient-level data from a phase III trial of topotecan and cisplatin (GOG-0179)[5]. Trial GOG-0179 included a wider population than that in which topotecan is licensed[1,6] and so the cost-utility analysis has been conducted using re-analysed data from those subjects in the trial that meet the licensed indication. Further subgroup analyses (cisplatin-naïve patients and those previously exposed to cisplatin 180 days or more before recurrence of disease [sustained cisplatin-free interval, SCFI]) have also been undertaken. These approaches would seem appropriate but it should be noted that these were *post hoc* analyses and the power of the study to detect true differences in effect between the treatment regimens in the sub groups is reduced, as noted in the company submission[5]. In addition, these re-analysed data are not provided or referenced and so verification of the data is not possible beyond what is contained within the company submission. This model has not been provided by the company.

The secondary "indirect" cost-effectiveness analysis compares data from trial GOG-0179 with that obtained from a trial of paclitaxel plus cisplatin versus cisplatin alone (GOG-0169)[5,12]. Patient-level data were not available from trial GOG-0169 and so data from the whole intention to treat population (including patients not meeting the licensed indication for topotecan) were compared with cisplatin-naïve patient data from GOG-0179 (including a small number of patients with persistent cervical cancer outwith the licensed indication for topotecan). No utility values were applied to the survival data from GOG-0169. Therefore, the modelled cost-effectiveness refers to the incremental cost per life year gained for topotecan plus cisplatin versus paclitaxel plus cisplatin, which is a relatively expensive and apparently uncommonly used regimen in Wales[5], in a subgroup of patients who may not fully meet the licensed indication for topotecan. Therefore, there are several issues which limit the usefulness of this analysis. This model has been provided by the company.

A cost analysis of other chemotherapy regimens commonly used in Wales (cisplatin alone, bleomycin plus mitomycin-C plus cisplatin [BMC], carboplatin alone, and carboplatin plus paclitaxel) is also presented. The basis of the analysis is that there is a lack of robust evidence of superiority of these chemotherapy regimens over cisplatin (i.e. no randomised trials of these regimens versus cisplatin-based regimens have been conducted in this patient group with the necessary power to detect differences in overall survival, etc.). However this analysis needs to be treated with extreme caution

as, in effect, it represents a cost-minimisation analysis without supporting evidence on therapeutic equivalence.

2. Population

The patient data used in the primary cost-utility analysis appropriately cover the licensed indication for topotecan in cervical cancer[1]. The company submission notes that the distributions of performance status (PS) of patients in the subgroups, however, was uneven in the topotecan-treated arms: in the SCFI population proportionately fewer patients had a PS of 0 (PS 0:1:2, 43%:51%:6% versus 47%:42%:11% for cisplatin) whilst in the cisplatin-naïve population proportionately more patients had a PS of 0 (PS 0:1:2, 60%:33%:7% versus 48%:47%;5% for cisplatin)[5] . The extent to which this would influence the results (e.g. patients with a better PS may respond better to chemotherapy) is unclear and is not explored in the analyses.

The secondary "indirect" analysis populations do not fully meet the licensed indications for topotecan and it is not possible to extract the results that relate specifically to the relevant patient population (see section 1. above)[1]. In addition, the distribution of the PS of the cisplatin-naïve population taken from trial GOG-0179 and the ITT population of trial GOG-0169 is uneven: the proportion of patients with PS 0:1:2 was 61%:31%:8% for topotecan-treated patients versus 45.4%: 41.5%:13.1% for paclitaxel-treated patients[5]. This potentially favours the topotecan-treated group from trial GOG-0179 as they had, as a group, a better performance status and so may have responded better to chemotherapy than the ITT population from trial GOG-0169.

3. Perspective and time horizon

The model considers costs from the perspective of NHS Wales[5]. No consideration is given to any personal and social service costs/resources.

A time horizon of 36 months was used for the cost-utility analysis in the broad population that meets the licensed indication for topotecan and in the subgroup of *cisplatin-naïve* patients. This time horizon was based on the time to the last known deaths of patients in these groups in trial GOG-0179, which were 31 months for those receiving topotecan plus cisplatin and 34 months for those receiving cisplatin alone. Based on Kaplan-Meier curves, the probability of survival at these points was 0.05 for the topotecan plus cisplatin treated patients and 0.017 for patients treated with cisplatin[5]. The analysis assumes that these survival rates remained constant up to 36 months in each treatment arm. The impact of this is unclear, as it assumes a longer, more sustained survival for topotecan plus cisplatin than for cisplatin alone (i.e. a 5% probability of survival over four months for topotecan plus cisplatin, compared with a 1.7% probability of survival for cisplatin alone over two months). It should be noted that patient numbers in the trial at this time point were small, which would be especially relevant when considering *post hoc* defined subgroups.

For the SCFI subgroup of patients, a time horizon of 18 months has been considered based on the last known deaths in both treatment arms occurring at 17 months[5]. At this point, the probability of survival was 8% for the topotecan-treated group and 4% for patients treated with cisplatin alone. For the secondary "indirect" analysis, a time horizon of 24 months was used as trial GOG-0169 had follow-up data only to 24 months[5,12]. Therefore, only 24 month data for topotecan plus cisplatin was used[5].

4. Comparator

There are several different chemotherapy regimens employed in the treatment of cancer of the cervix. The company submission includes data on treatment patterns obtained from three oncologists who, it is stated, treat nearly all patients with recurrent and stage IV-B cervical cancer in Wales[5].These data indicate that cisplatin monotherapy is used in a minority (approximately 7.5%) of the relevant patient population in Wales, with BMC being used in approximately 42.5%, carboplatin monotherapy in approximately 33.3% and carboplatin plus paclitaxel in the remainder (approximately 16.7%). Excluding cisplatin monotherapy, these regimens are unlicensed in this patient group.

Trial GOG-0179, used to provide the data for the primary cost-utility analysis, compared topotecan plus cisplatin versus cisplatin alone[5]. Whilst topotecan and cisplatin are licensed agents for this patient group[1],the analysis is limited as it does not describe the cost-utility of topotecan plus cisplatin relative to the treatment regimens used in the majority of cases currently treated in Wales. The secondary "indirect" analysis also does not, as paclitaxel plus cisplatin (used in trial GOG-0169)[4] is not a well used regimen in Wales in this population (according to the expert opinion of Welsh oncologists, as presented in the company submission)[5].

This represents a serious limitation on the evidence presented: the comparators chosen for the economic evaluation are not representative of current practice in Wales.

No robust evidence is presented in the company submission to support the suggestion that the cost-utility of topotecan plus cisplatin versus cisplatin is broadly representative of the cost-utility of topotecan plus cisplatin versus BMC or versus carboplatin (nor the suggestion that the indirect analysis is representative of the cost-effectiveness of topotecan plus cisplatin versus carboplatin plus paclitaxel).

5. Clinical inputs

5.1 Efficacy data

For the primary cost-utility analysis, patient-level data from trial GOG-0179 have been re-analysed to derive survival estimates (all-cause mortality) in the licensed population, and in the subgroups of the licensed population: the cisplatin-naïve population and the SCFI population. Median overall survival was statistically significantly greater with topotecan plus cisplatin versus cisplatin alone in the licensed population (11.9 versus 7.3 months, hazard ratio [HR] 0.652 [95% CI: 0.485 to 0.875]) and the cisplatin-naïve population (14.5 versus 8.5 months, HR 0.587 [95% CI: 0.389 to 0.884]), but not the SCFI population (9.9 versus 6.3, HR 0.75 [95% CI: 0.492 to 1.155])[5]. However, *post hoc* subgroup analyses should be viewed with caution. In addition, the PS of patients is unevenly distributed in the topotecan-treated patients in the SCFI population and the cisplatin-naïve population (see 1. and 2. for a discussion of issues with the efficacy data).

For the secondary "indirect" cost-effectiveness analysis, data from the cisplatin-naïve population of trial GOG-0179 (including a small number of patients with persistent cervical cancer outwith the licensed indication for topotecan) were compared with those obtained from the ITT population of trial GOG-0169 (paclitaxel plus cisplatin versus cisplatin alone)[5] . The HR for paclitaxel plus cisplatin versus cisplatin alone, calculated as 0.87 [95% CI 0.68 to 1.11], was applied to the observed overall survival for cisplatin-treated patients in trial GOG-0179 to estimate the overall survival for paclitaxel plus cisplatin for the indirect comparison with topotecan plus cisplatin[5]. There were several differences between the populations of trials GOG-0179 and GOG-

0169. For example, fewer patients in GOG-0169 had received radiosensitising chemotherapy (approximately 27% versus approximately 60%), which may have influenced their potential to respond to subsequent chemotherapy; and the PS distributions of the patient populations were uneven (see sections 1. and 2. above)[5]. How adequately the use of this HR to "transform" the data from trial GOG-0179 addresses these issues is unclear.

5.2 Utility values in the primary analysis

Quality of life (QoL) was assessed in patients in trial GOG-0179 using the FACT-G (Functional Assessment of Cancer Therapy – General) tool, which was administered four times throughout the study (at baseline, before the second and fifth cycles of chemotherapy, and at 9 months after randomisation)[5,13]. However, the base-case of the primary cost-utility analysis uses utility values derived from published estimates of nurses in relation to metastatic breast cancer[11].

Utility values relating to the "health states" of the start of treatment, response, progression and specific haematological adverse effects have been applied. For the haematological adverse effects, only those related to febrile neutropenia resulting in a dose reduction, and thrombocytopenia requiring platelet transfusion, were classed as decreasing utility values (and the decrease in utility values for thrombocytopenia was assumed to be the same as for febrile neutropenia). Although the views of oncologists were sought it is unclear how reliable this assumption is[5]. Utility decreases associated with these adverse events were applied for week-long intervals only, in line with clinical opinion.

There are obvious limitations to the breast cancer treatment utility values being used in terms of their applicability to the cervical cancer patient population. In addition, the utility values taken from the published breast cancer study have been inconsistently applied. All utility values used in the model, with the exception of those relating to the adverse event of febrile neutropenia, are derived from the average utility values estimated by nurses from six countries. These are seen to be generally lower than those estimated by nurses from the US only[11]. However, for the adverse event of febrile neutropenia, the utility values estimated by nurses from the US only are assumed in the model, and these utility values are higher than the average values estimated by nurses from six countries (0.42 versus 0.30). Subsequent communication with the manufacturers revealed that this was as an error on their part, and that the use of correct figures did not affect the overall cost per QALY gained appreciably. The utility values derived from FACT-G data in trial GOG-0179 were used in a sensitivity analysis[5].

5.3 Adverse events

For the primary analysis, only two haematological adverse effects were considered to decrease utility in the patient group for the primary cost-utility analysis, as discussed in 5.2 above. Non-haematological adverse events were not considered to have an impact on utility values, but serious treatment-related adverse events have been costed (see section 6).

For the secondary "indirect" analysis, the overall observed rates of grade 3 and 4 haematological adverse events (neutropenia, thrombocytopenia and anaemia) from the ITT population in trial GOG-0169 and the cisplatin-naïve population (plus a small number of patients with persistent disease in trial GOG-0179) were used in the costings. Utility values are not considered in this analysis.

6. Healthcare resource utilisation and cost

6.1 Chemotherapy, other medications and follow-up

6.1.1 Primary analysis

Chemotherapy regimens are costed on the basis of patient-level data with the exception of mean body surface area (assumed to be 1.7m^2, as used in recent NICE technology appraisals in ovarian cancer and breast cancer)[5]. The topotecan SPC states that vials should be discarded 24 hours after opening but the company submission states that communication with pharmacists (no further details provided) suggests practices range widely in this regard[1,5]. Therefore, minimum and maximum wastage of topotecan vials is explored in sensitivity analyses, with some re-use (approximately the mid-range) used in the base-case analysis. For cisplatin, maximum wastage is assumed, which is likely to be conservative. The influence of dose modification for topotecan is incorporated.

Other costs in the analysis include hydration treatment for use with cisplatin, and the costs of pharmacy, nurse and day case attendance/outpatient visits. Pre- and post-treatment antiemetic medication and steroid has been incorporated (with topotecan recipients receiving pre-treatment on days one, two and three of each cycle, and cisplatin monotherapy recipients receiving pre-treatment on day one only). Although practices vary across Wales, the antiemetic regimen included is stated to be broadly in line with those used across Wales (referenced to personal communications with oncologists)[5]. It is assumed that the regimen costed in this analysis has the same efficacy as in trial GOG-0179. Follow-up costs have been incorporated, in line with Welsh oncologist practice.

Costs appear to have been appropriately derived from NHS National Reference costs, PSSRU and BNF, as well as previous technology appraisals, and Welsh oncologists have confirmed that assumptions used are reasonable[5].

6.1.2 Secondary "indirect" analysis

The cisplatin and topotecan costs assumed in the secondary analysis were based on those used in the primary analysis, with the exception that dose modification was not considered; mean number of cycles have been used for costing rather than patient-level data[5].

Paclitaxel is assumed to be given using the most efficient combination of vial sizes to provide the recommended dose.The price of generic paclitaxel is used in the base case and sensitivity analysis was conducted using 50% of the price of branded paclitaxel. The base-case vial wastage scenario described for topotecan in the primary analysis is used in the secondary analysis. The mean number of cycles of treatment for cisplatin monotherapy (4.23) was taken from the cisplatin-naïve patient population in trial GOG-0179. The mean number of cycles of topotecan plus cisplatin (5.125) was taken from the same population, and the mean number of cycles of paclitaxel is assumed to be the same as this as the median number of cycles of cisplatin and paclitaxel plus cisplatin were 4 and 5 respectively in trial GOG-0169[12].

6.2 Adverse events

Adverse event data for the primary analysis had to be collated from laboratory and intervention reports, as the adverse event dataset reported the occurrence but not the frequency of adverse events. It was assumed that the majority of non-haematological adverse events would not require intervention and therefore these were not costed. Serious treatment-related non-haematological adverse events were included, with costs attached based on NHS Reference Costs[5].

For the indirect analysis, the overall observed rates of grade 3 and 4 haematological adverse events (neutropenia, thrombocytopenia and anaemia) from the ITT population in trial GOG-0169 and the cisplatin-naïve population (plus a small number of patients with persistent disease in trial GOG-0179) were used in the costings. Non-haematological adverse events are not considered, but the available data do not suggest significant differences between the regimens in this respect[5,12].

7. Discounting

All costs and outcomes were discounted at 3.5% in the base case analysis, which is the preferred discount rate.

8. Results

8.1. Primary analysis[5]

Incremental Cost per QALY gained

	Base-case analysis	Sub-group analyses	
	Licensed population 36-month time horizon	**Cisplatin-naïve sub group 36 month time horizon**	**SCFI sub group 18 month time horizon**
Incremental Cost per QALY gained	£24,115 (£4,067 / 0.17 QALYs)	£15,543 (£3,482 / 0.22 QALYs)	£34,076 (£4,081 / 0.12 QALYs)

All costs and outcomes discounted at 3.5% per annum

In the whole licensed population, the base-case analysis indicates a cost per QALY gained of £24,115 for topotecan plus cisplatin versus cisplatin alone. In the cisplatin-naïve sub group, the ICER reduces to £15,543 as costs are lower and the QALY gains higher than the base case. However, in the cisplatin-experienced subgroup, the ICER increases to £34,076, primarily due to reduced QALY gains[5].

8.2 Secondary "indirect" analysis

Paclitaxel plus cisplatin was dominated by topotecan plus cisplatin on the basis of higher costs and lower effectiveness (incremental costs over topotecan plus cisplatin were £285 and mean life-years were lower by 0.17). For topotecan plus cisplatin versus cisplatin alone, the incremental cost per life year gained was £19,768 over a 24 month time horizon of analysis[5].

9. Sensitivity analysis

One-way sensitivity analyses were carried out in the primary and secondary "indirect" analyses. Probabilistic sensitivity analysis was conducted in the primary analysis only[5].

9.1 Sensitivity analyses in the primary analysis

The use of trial-derived utility values instead of the literature-based breast cancer treatment utility values reduced the ICER in all groups, but less so in the SCFI population[5]. As patients were not blinded to therapy, there is a potential for bias, and favourable reporting of health outcomesThe other one-way sensitivity analyses simply describe scenarios of increasing or decreasing the costs of topotecan-associated treatment. The results of which are as would be expected:

	Incremental cost per QALY gained		
Parameters:	**Licensed population 36 month time horizon**	**Cisplatin-naïve sub group 36 month time horizon**	**SCFI sub group 18 month time horizon**
Use of trial derived (FACT-G) utility values	£17,736	£10,808	£31,963
Minimal wastage of topotecan vials	£22,097	£14,040	£31,773
Maximum wastage of topotecan vials	£26,127	£17,036	£36,378
Pre-treatment Medication on day 1 only for topotecan-recipients	£22,920	£14,674	£32,757

Bootstrap methods were used for the probabilistic sensitivity analysis (PSA). The PSA resulted in the bootstrap mean ICER increasing slightly for the licensed population but decreasing for the subgroups compared with the base case analysis results (the ICER for the SCFI population appeared to decrease by around 13%)[5] .

The probabilities of topotecan plus cisplatin being cost-effective at willingness to pay (WTP) thresholds of £20,000 and £30,000 per QALY gained in the base case analysis were 0.27 and 0.61, respectively. The use of the FACT-G utilities resulted in higher probabilities of cost-effectiveness for all populations[5].

	Licensed population 36 month time horizon	**Cisplatin-naïve sub group 36 month time horizon**	**SCFI sub group 18 month time horizon**
Bootstrap mean Incremental cost/QALY	£25,939	£13,722	£29,551
Probability cost-effective @ WTP £20,000/QALY	0.27 (literature utilities) 0.55 (FACT-G utilities)	0.74 (literature utilities) 0.89 (FACT-G utilities)	0.21 (literature utilities) 0.43* (FACT-G utilities)
Probability cost-effective @ WTP £30,000/QALY	0.61 (literature utilities) 0.82 (FACT-G utilities)	0.90 (literature utilities) 0.96 (FACT-G utilities)	0.54 (literature utilities) 0.65* (FACT-G utilities)

All costs and outcomes discounted at 3.5% per annum

* These figures do not correspond with the values suggested from reading off the cost effectiveness acceptability curves

9.2 One-way sensitivity analysis in the secondary "indirect" analysis

The impact of reducing the cost of paclitaxel to 50% of the branded price was explored. The cost of paclitaxel plus cisplatin was then lower than the cost of topotecan plus cisplatin but the direction of the result remained the same. The ICER for paclitaxel plus cisplatin versus cisplatin monotherapy was £48,078 per life-year gained. For topotecan plus cisplatin versus paclitaxel plus cisplatin, the ICER was £8,239 per life-year gained. Paclitaxel plus cisplatin was therefore eliminated on the grounds of extended dominance[5].

Company submission - budget impact analysis

1. Description and critique of the company submission

The company submission considers the impact of the use of topotecan plus cisplatin in patients with stage IV-B or recurrent (after radiotherapy) carcinoma of the cervix in line with the licensed indication[1,5] .

2. Perspective and time horizon

The perspective adopted by the budget impact analysis is that of NHS Wales, with a five-year time horizon[5].

3. Data sources

3.1. Incident cases

A prevalence-based approach has been used, as mortality is approximately 100% and the projected increase in incidence (0.2% per annum) has been considered small enough to be negligible[5].

3.2 Prevalent cases

The company submission states that there would be around 30 patients meeting the licensed indication for topotecan in Wales each year. This has been estimated by working backwards from the number of deaths in Wales from 2005 (73 deaths). It is assumed that the proportion of women with persistent cancer in Wales would be the same as in the population of trial GOG-0179 (11%), which would mean that 89% (65 patients) would have recurrent and stage IV-B cancer. 75% of these patients have been estimated to be eligible for chemotherapy, based on expert opinion (equivalent to 49 patients). Of these, 60% (30 patients) have been estimated to be either cisplatin-naïve or to have had a SCFI, again based on expert opinion[5].

3.3 Rates of adoption, market share and displaced medicines

The company submission notes that, currently, these patients are treated with cisplatin alone (7.5%), BMC (42.5%), carboplatin (33.3%) and carboplatin plus paclitaxel (16.7%). These data are based on the treatment regimens used by three oncologists in Wales who, it is stated, treat nearly all of the patients[5].

The company submission assumes that topotecan would be adopted in 40% of eligible patients in year 1, rising to 80% in year 5, with replacement of the current chemotherapy regimens in equal proportions[5].

4. Results

4.1 Base-case

The direct costs considered in the analysis include the costs of chemotherapy and administration costs including hospital attendances, pharmacy costs and pre- and post-treatment medication. It is assumed that topotecan-treated patients receive three days of pre-treatment. The mean number of cycles of topotecan plus cisplatin (4.54) and cisplatin alone (3.92) are based on the licensed population group of trial GOG-0179. The mean number of cycles of treatment with BMC and carboplatin alone are assumed to be the same as cisplatin alone, and for paclitaxel plus carboplatin it is assumed to be the same as for topotecan plus cisplatin[5].

Based on reported current prescribing patterns across the whole of Wales, uptake of topotecan in year 1 (40%) would increase costs by £26,684, rising to £53,369 in year 5 (80%).

4.2 Sub-group analysis

Two other scenarios have been modelled:

Based on current prescribing of cisplatin regimens (15% cisplatin alone or 85% BMC, as used by one of the Welsh oncologists) in half of all eligible patients (i.e. 15 patients), uptake of topotecan in year 1 (40%) would increase costs by £17,910, rising to £35,820 in year 5 (80%)[5].

Based on current prescribing of carboplatin regimens (67% carboplatin alone or 33% paclitaxel plus carboplatin, as used by one of the Welsh oncologists) in half of all eligible patients (i.e. 15 patients), uptake of topotecan in year 1 (40%) would increase costs by £8,775, rising to £17,549 in year 5 (80%)[5] .

5. Sensitivity analysis

No sensitivity analysis has been conducted.