All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

AWMSG ADVICE SUPERSEDED BY NICE GUIDANCE (TA184)

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Final Appraisal Report

Intravenous topotecan (Hycamtin®)

GlaxoSmithKline UK Ltd.

Advice No: 0108 – February 2008

Recommendation of AWMSG

Intravenous topotecan (Hycamtin®) is recommended for use within NHS Wales for the treatment of patients with relapsed small cell lung cancer (SCLC) for whom re-treatment with the first-line regimen is not considered appropriate.

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

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 Small Cell Lung 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 for the treatment of patients with relapsed small cell lung cancer (SCLC) for whom re-treatment with the first-line regimen is not considered appropriate**.**

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

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

Key factors influencing the recommendation:

The AWMSG recommendation is based on consideration of the evidence submitted by all stakeholders.

2.0 PRODUCT DETAILS:

2.1 Licensed indication:

Topotecan (Hycamtin®) is indicated for patients with relapsed small cell lung cancer (SCLC) for whom re-treatment with the first-line regimen is not considered appropriate[1].

2.2 Dosing:

The recommended dose of topotecan for SCLC is 1.5mg/m^2 body surface area/day administered by intravenous (IV) infusion over 30 minutes daily for five consecutive days, with a three-week interval between the start of each course. If well tolerated, treatment may continue until disease progression[1].

2.3 Market authorisation date: 13th January 2006[2]

2.4 UK Launch date: 13th January 2006

3.0 DECISION CONTEXT

This appraisal focuses on topotecan treatment for SCLC. Topotecan is also licensed for ovarian cancer and cervical cancer[1]. NICE has issued guidance on topotecan for the second line treatment of ovarian cancer[3]. Cervical cancer is the subject of AWMSG appraisal number 0208.

Lung cancer is one of the most commonly occurring malignant diseases. SCLC represents approximately 14% of all lung cancers and is a devastating disease with a long-term survival rate of around 5%. Most patients already have extended disease at first diagnosis although there is usually an initial response to chemotherapy albeit a rapid development of resistance to treatment[4]. Objective response (OR) rate and symptomatic control varies as to whether a patient has limited or extensive disease. To date, combination chemotherapy has been shown to give better OR rates and symptom control than single agent chemotherapy in limited disease and be less toxic and more effective than treatment with the single agent etoposide in extensive disease[5].

In addition to active symptom control (ASC), patients with SCLC are treated with a suitable first line regimen (cisplatin/carboplatin and etoposide) or CAV (cyclophosphamide, Adriamycin® (doxorubicin) and vincristine)[4].

The majority of patients with SCLC who are treated with standard chemotherapy experience relapse within one year of treatment[7]. Patients who have responded to first line chemotherapy and who have had at least six month's disease-free survival are most likely to benefit from second line treatment[5]. Patients within the United Kingdom are usually treated with anthracycline based regimens as a second-line chemotherapy; either CAV or ACE (doxorubicin, cyclophosphamide, etoposide)[2].

Patients who do not receive chemotherapy are currently managed with ASC alone. However, all patients receive ASC routinely, either alone or in addition to chemotherapy, as a standard part of their management. ASC includes:

- Prescription of analgesics for pain, antibiotics for infection, and antidepressants.
- Provision of palliative radiotherapy, deep relaxation therapy and palliative surgical procedures.

ASC excludes chemotherapy, cytokine therapy or use of research drugs including inhibitors of angiogenesis or anti-tumour vaccines[6].

CAV and ACE regimens both contain the anthracycline doxorubicin (Adriamycin®) [8]. Higher cumulative doses are associated with cardiomyopathy and it is usual to limit total cumulative doses to 450 mg/m^2 because symptomatic and potentially fatal heart failure is common above this dose[8]. Within the subset of patients who are managed with ASC alone there are a group of patients who do not receive CAV or ACE because of their cardiovascular risk profile (e.g. heart failure, acute coronary syndrome).

Topotecan is a cytotoxic agent; a semi synthetic analogue of the alkaloid camptothecin. Topotecan exerts its activity by the inhibition of the nuclear enzyme topoisomerase I that is involved in DNA replication[4]. The company submission proposes that topotecan would be an appropriate treatment option for patients who would be considered unsuitable to receive an anthracycline based regimen (those with pre-existing cardiovascular conditions) but who are eligible for second line SCLC chemotherapy[6].

4.0 EXECUTIVE SUMMARY:

4.1 Review of the evidence on clinical effectiveness

Study 478 showed that oral topotecan with ASC has a beneficial effect when compared with ASC alone in treatment resistant SCLC patients. This oral topotecan and ASC group had a progression free interval of at least 45 days. As the comparator was ASC alone it is likely that the patients included in this study had a very poor prognosis anyway, but it was not made clear why patients were not considered suitable for further IV chemotherapy.

The results of study 396 showed similar efficacy with regards to response rate between the oral and IV formulations of topotecan. The company submission assumes that we can also draw the same conclusions with regard to the benefits and disadvantages of IV topotecan where oral topotecan plus ASC is used instead of ASC alone.

Study 478 showed that oral topotecan plus ASC treatment resulted in a better quality of life (QoL) (higher EQ-5D questionnaire scores) and a slower rate of decline in QoL than treatment with ASC alone. The submission suggests that results of study 396, which show that IV and oral topotecan have similar efficacy, that these QoL benefits are directly applicable to IV topotecan. Patients treated with oral topotecan and ASC needed fewer palliative medications and less radiotherapy than those treated with ASC alone.

The evidence from study 396 indicates that oral and IV topotecan are broadly similar with respect to the incidence of haematological toxicities, non-haematological adverse events (AEs), serious adverse events (SAEs) and study withdrawals due to AEs. Study 478 reported higher incidences of haematological toxicity, haematologically related SAEs, and AE related study withdrawals in the topotecan plus ASC group, while the incidence of disease progression was higher in the ASC only group of participants. The overall incidence of haematological toxicity and its consequences did not increase in the elderly but it did to some extent in patients with poor performance status (PS).

4.2 Review of the evidence on cost-effectiveness

The company submission details a cost-effectiveness and cost-utility analysis of intravenous topotecan plus active symptom control (ASC) versus ASC alone, in

patients with small cell lung cancer (SCLC) for whom second line chemotherapy is considered suitable, but an anthracycline-based regimen is judged to be inappropriate.

The analysis is based on the results of study 478, which compares oral topotecan plus ASC with ASC alone. Recruitment to study 478, however, did not require patients to be unsuited for anthracycline-based regimens. Moreover, patients were excluded from study 478 if they were deemed unsuitable for intravenous chemotherapy.

The company assumed therapeutic equivalence of intravenous and oral topotecan based on the findings of study 396. It is important to note that the population included in studies 478 and 396 are different in terms of patients' resistance / sensitivity to first-line chemotherapy.

The economic analysis may therefore be based on a population that may be somewhat different from that stated in the decision problem.

The total per-patient cost of intravenous topotecan therapy is divided between £3,539 for drug acquisition, £1,660 for drug administration and £498 for the management of adverse events.

The incremental cost per life-year gained of intravenous topotecan plus ASC, relative to ASC is £21,302. The corresponding incremental cost per QALY gained is £23,660.

5.0 LIMITATIONS OF DECISION CONTEXT:

- There is limited evidence for the clinical benefit of any second line therapy in SCLC[9].

- This submission suggests that topotecan has similar efficacy to the CAV regimen, with the advantage of superior symptom control, although this trial was not included as a pivotal trial to support the submission[6].

- Study 478, which compares oral topotecan and ASC to ASC alone, does not make it clear why patients were considered unsuitable for further IV chemotherapy. Therefore the trial patients may not be representative of those who are eligible for IV topotecan.

- It is important to note that the population included in studies 478 and 396 are different with regard to patient resistance and sensitivity to first-line chemotherapy. Study 478 was designed to recruit resistant patients and Study 396 was designed to recruit sensitive patients (see Appendix 1 for definitions).

- Primary efficacy endpoints differed between studies included in the company submission. Overall survival was the primary efficacy endpoint in Study 478, whereas in Study 396 it was response rate.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

6.1 Clinical efficacy:

The company has submitted two pivotal trials (Studies 396 and 478) to support the case that IV topotecan is as active as oral topotecan in relapsed sensitive SCLC and that topotecan plus ASC is superior to ASC alone. For both trials, patients were eligible if they were ≥ 18 years, had received one prior chemotherapy regimen only, had documented partial or complete response to first-line therapy and an Eastern Co-operative Study Group (ECOG) performance status (PS) score of two or less[6].

6.1.1 Phase III study – topotecan IV versus topotecan oral (study 396) [10]

This open label, multi-centre, randomised Phase III study was designed to compare the clinical profile of IV topotecan with oral topotecan as second line therapy in patients with advanced SCLC who have relapsed at least 90 days after completion of first-line chemotherapy. The oral formulation of topotecan is not currently licensed in the UK.

The initial dose of oral topotecan was 2.3mg/m^2/day for five consecutive days every 21 days (n=153). The initial dose of IV topotecan was 1.5mg/m^2/day given as a 30 minute infusion for five consecutive days every 21 days (n=151)[5].

Concomitant radiotherapy was permitted for control of bone pain or brain lesions[10], but not all measurable lesions were to be included in the irradiated field as this could interfere with analysis of chemotherapy effects[6].

At total of 309 patients were randomly assigned to treatment: 153 to oral topotecan and 151 to IV topotecan (five patients received no treatment).

The primary efficacy measure was response rate, defined as the percentage of patients achieving either a complete or partial response to chemotherapy. As the study objective was to demonstrate non-inferiority of oral to IV topotecan, the lower limit of the 95% confidence interval (CI) was compared against a pre-specified margin of non-inferiority (10%)[6].

Secondary efficacy measures were time to response, response duration, time to progression, survival and quality of life (Appendix 1, table 1 details definition of secondary efficacy measures). Quality of life was assessed using the Functional Assessment of Cancer Therapy-G and Lung Cancer Subscale [FACT-L] [6].

Results:

According to the paper by Eckardt and colleagues, the proportion of patients completing therapy was similar for both oral (124 patients; 81%) and IV topotecan (128 patients; 85%) treatment arms. The company submission however states that 122 and 127 patients, respectively, completed therapy[10].

Table 1. Primary efficacy endpoint results – best response rate[6]

Response	Oral Topotecan (n=53)		IV Topotecan (n=151)	
	No. of patients	%	No. of patients	%
Responders				
Complete response	2	1.3	0	0
Partial response	26	17	33	21.9
Overall response	28	18.3	33	21.9
95% CI, (%)	12.2 to 24.4		15.3 to 28.5	
Non-responders				
Stable disease	27	17.6	35	23.2
Progressive disease	78	51	65	43
Not assessable *	20	13.1	18	11.9

* The patients who were not assessable for response were those who died, were withdrawn (as a result of an adverse experience or a protocol violation), withdrew consent after one or two courses of treatment or were considered to have completed treatment after one or two courses.

The difference in response rates (oral to IV) was -3.6% (95% CI: -12.6% to 5.5%)[10].

For patients who responded to treatment with oral topotecan, median time to response in the ITT population was 6.1 weeks and median duration of response was 18.3 weeks compared to 6.1 weeks and 25.4 weeks respectively for the IV group. The median time to progression in the oral topotecan group was 11.9 weeks compared to 14.6 weeks for those receiving IV topotecan (Hazard Ratio: 1.28, 95% CI: 1.01, 1.63) [6].

Median survival times in this study were 33.0 weeks (95% CI: 29.1 to 42.4) for oral topotecan and 35.0 weeks (95% CI: 31.0 to 37.4) for IV topotecan[10]. The hazard ratio of oral topotecan relative to IV topotecan for survival was 0.98 (95% CI: 0.77 to 1.25), indicating no significant difference for the two treatments[10]. Comparison of survival outcomes was not affected by post-study third-line chemotherapy as a similar proportion of patients in both treatment groups received third-line therapy (chemotherapy; IV: 35%, oral: 33%). There was no significant difference in quality of life assessment between oral and IV treatments in change from baseline in total FACT-L scores [6,10].

Points to note

- This study recruited sensitive patients: those who had progressed greater than or equal to 90 days after having a documented response to first line therapy.
- The oral group had a lower proportion of patients with poorer performance status (PS 1 and 2) than the IV topotecan group (68.7% versus 76.8%), although this may not be considered to be clinically significant [6,10].
- The company submission highlights that interpretation of the time to progression results is limited by the fact that the patients were not monitored consistently with respect to frequency or methodology of assessment, and that this secondary endpoint was not independently confirmed[6].
- The oral formulation of topotecan is not licensed in the UK for any indication[6].

6.1.2 Phase III study – oral topotecan plus ASC versus ASC (study 478)[7]

This was an open-label, multi-centre, randomised Phase III trial in 141 patients who were not considered suitable for further intravenous chemotherapy and had documented relapse of limited or extensive SCLC at least 45 days after the cessation of first-line chemotherapy. The ITT population (all randomised patients) comprised 71 patients in the oral topotecan plus ASC group and 70 patients in the ASC alone group. Patients were stratified according to time to progression (TTP) from end of chemotherapy (60 days and less, or more than 60 days); performance status (0/1 or 2); gender, and liver metastases (present or absent) [6].

The dosage of oral topotecan was the same as for study 396. ASC included all palliative and supportive treatments: analgesics, antibiotics, corticosteroids, appetite stimulants, antidepressants, blood transfusions, relaxation therapy, palliative radiotherapy or surgical procedures[7].

The primary efficacy outcome was overall survival (all-cause mortality) expressed as the time from randomisation until death. Secondary efficacy outcome measures included response rate, time to progression, control of disease symptoms and quality of life (Appendix 1, table 2 details definitions of secondary efficacy measures)[6].

Results:
The median overall survival in the oral topotecan plus ASC group was 25.9 weeks (95% CI: 18.3 to 31.6) compared to 13.9 weeks (95% CI: 11.1 to 18.6) in the ASC alone group. The unadjusted hazard ratio (HR) for oral topotecan plus ASC relative to ASC alone was 0.638 (95% CI: 0.45 to 0.90), indicating a 36% reduction in the risk of death for the oral topotecan plus ASC group[5]. The HR adjusted for the stratification factors was 0.608 (95% CI: 0.43, 0.87). Adjusted HR for survival comparing patients whose time to progression was less than or equal to 60 days, to those whose time progression was greater than 60 days was 1.19 (95% CI: 0.81, 1.76)[6].

Secondary efficacy endpoints demonstrated, 43.7% (31/71) of patients in the oral topotecan plus ASC group achieved stable disease and five out of 71 patients (7.0%) had a partial response to treatment. No patients had a complete response[6]. Median time to progression for these patients was 16.3 weeks (95% CI: 12.9, 20). In the ASC alone group 18 out of 70 (25.7%) patients were alive after six months, compared to 34 out of 71 (48.9%) patients in the topotecan plus ASC group.

The rate of deterioration over three months in EQ-5D was -0.05 (95% CI: -0.11 to 0.02) and -0.20 (95% CI: -0.27 to -0.12) for the oral topotecan plus ASC and ASC alone groups respectively. The topotecan plus ASC group had statistically significant reductions in shortness of breath, interference with sleep and fatigue compared with ASC alone[5]. The median TTP for the oral topotecan plus ASC group was 16.3 weeks (95% CI: 12.9 to 20.0) and was not reported in the ASC alone group [6,7].

Palliative medication for SCLC symptoms was used more frequently in the ASC alone group than the topotecan plus ASC group (82% and 60% of patients respectively). Transfusions were required more frequently in the topotecan group (33%) when compared to ASC alone (10%). Appendix 1, table 3 illustrates the palliative care treatments given[6].

Points to note

- The European Public Assessment Report (EPAR) states that survival is considered as the only acceptable primary endpoint in confirmatory studies in SCLC[4].

- This study was designed to recruit resistant patients; i.e. those who had achieved a partial or complete response to first line therapy and progressed at least 45 days after completing first line therapy, who were not candidates for further IV chemotherapy but were considered of sufficient good health to tolerate treatment with single agent oral topotecan.

- Patients were excluded from this study if they were deemed unsuitable for further IV chemotherapy, although reasons for this are unclear.

- As the median survival of the treated group was 25.9 weeks, approximately 50% of these patients in both arms had a good PS of 0 to 1 at study entry, and an average of 50% of patients had a treatment free interval of longer than 90 days, this group of patients could have been offered standard IV chemotherapy in clinical practice[7].

- The EPAR states that, as would be expected, the natural course of the untreated disease is that patients with a better PS have a longer survival without treatment than patients with a lower PS (18.6 weeks versus 7.7 weeks respectively). Both groups of patients (PS 0/1 and PS 2) experienced survival benefit following treatment with active chemotherapy. For patients with PS 0/1 the median survival following active chemotherapy was 29.2 weeks and for patients with PS 2, the median was 20.9 weeks[4].

- At six months the topotecan group showed improved survival rates compared to ASC alone (49% versus 26% respectively). The survival rates at one year were similar[7].

- Recruitment to this study did not require patients to be unsuitable for anthracycline-based regimens. Only 11.3% (n=8/71) of ITT patients in the oral topotecan and ASC treatment arm and 14.3% (n=10) of ITT patients in the ASC arm had pre-existing cardiovascular disorders[6].

- Although more patients in the ASC alone group received palliative medication than those treated with topotecan and ASC, more than half of patients (60%) in the topotecan group still required additional medication.

- The assumption of equivalence between IV and oral topotecan is based on the results of study 396.

- The oral formulation of topotecan is not licensed in the UK for any indication[6].

6.2 Safety:

The major adverse event (AE) associated with topotecan in relapsed SCLC is bone marrow suppression, which is reversible and manageable with dose adjustments. Nevertheless, there are major risk factors associated with the potential serious haematological toxicity of topotecan treatment[4].

In Study 396, the incidence of haematological toxicity, especially neutropenia, for IV topotecan was higher when compared to oral topotecan. The incidence of Grade 3/4 neutropenia was 88% in the IV population and 73% in the oral population. However, according to the EPAR, the increased incidence of neutropenia with the IV administration as compared to oral did not translate into a higher incidence of complications such as infection, sepsis and drug related mortality[4]. A total of 138 patients (90.2%) in the oral topotecan group and 136 patients (90.1%) in the IV topotecan group had non-haematological AEs, of any relationship to study treatment. In general the treatments were similar with respect to the incidence of individual AEs and the most commonly occurring events in both groups were nausea, fatigue and alopecia, together with diarrhoea [4,6] in the oral treatment group and dyspnoea in the IV group. Events were mainly mild to moderate in severity.

At the time of analysis (when all patients had at least one full course of treatment) 267 patients had died; 250 of them as a result of disease progression. Ten patients (six in the oral group and four in the IV group) died as a result of haematological toxicity, septic shock related to treatment with topotecan, or of other causes where a relationship to topotecan could not be excluded[9].

In Study 478, 27% (n=18/67) of patients in the ASC alone group and 26% (n = 18/70) of patients in the oral topotecan plus ASC group had serious adverse events (SAEs). Oral topotecan plus ASC patients had a higher incidence of all grade 3 and 4 SAEs (thrombocytopenia, leucopenia, neutropenia, neutropenic sepsis and diarrhoea), apart from disease progression, compared to ASC only. In addition, IV antibiotic use for fever, febrile neutropenia, or infections that were due to grade 4 neutropenia occurred in 8.6% (n=6/70) of topotecan plus ASC patients compared to 0/67 patients in the ASC only group[6].

The most frequent non-haematological AEs in the oral topotecan plus ASC group were nausea, vomiting and diarrhoea and the most frequent Grade 3/4 toxicity was diarrhoea. The most frequent AEs in the ASC alone group were disease progression, dyspnoea and cough and the most frequent Grade 3/4 toxicity was disease progression [4,6].

The European Medicines Agency has commented that “overall there are no new safety issues for topotecan when used in relapsed SCLC as compared with relapsed ovarian cancer. It has also been shown that there are no major differences regarding safety risks with IV topotecan as compared with oral”. It also states that “The Total IV Topotecan” (SCLC) population has demonstrated that a patient’s ability to tolerate therapy depends on a full recovery from first-line treatment, adequate bone marrow reserves, renal/hepatic function and performance status (PS) at the time of second-line therapy[4].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES:

7.1 Comparator medications:

No other treatment is currently licensed in the UK explicitly for the treatment of relapsed SCLC. In clinical practice patients are given anthracycline based regimens as a second-line chemotherapy; either CAV or ACE [2]. The company submission is specifically for topotecan for SCLC where second-line chemotherapy is considered suitable, but inappropriate with an anthracycline regimen because of pre-existing cardiovascular disease or contraindication. Patients however, are required to attend

the hospital clinic for five consecutive days each cycle to receive intravenous topotecan therapy[6], which may be a limitation particularly for those with a poor PS.

7.2 Comparative effectiveness:

There is limited evidence for the clinical benefit of any second line therapy in SCLC. Topotecan has a response rate and survival benefit which compares with that of the CAV regimen, but it has a greater toxicity in comparison with the CAV regimen. However, the comparative trial between topotecan and the CAV regimen was not submitted as a pivotal trial for consideration of the evidence. To date, there does not appear to be any significant differences in terms of response and survival rates in relation to the available options for second line treatment of SCLC[9].

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 intravenous topotecan over the relevant comparator justify any additional costs.

8.2 Review of published evidence on cost-effectiveness

No relevant published economic evidence relating to topotecan as second-line therapy for SCLC has been identified by standard literature searches conducted by the Welsh Medicines Partnership (WMP).

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8.3 Review of the company submission on cost-effectiveness

8.3.1 Summary of the evidence

The company submission details a cost-effectiveness and cost-utility analysis of intravenous topotecan plus active symptom control (ASC) versus ASC alone, in patients with small cell lung cancer (SCLC) for whom second line chemotherapy is considered suitable, but an anthracycline-based regimen is judged to be inappropriate[6]. The analysis is based on the results of study 478, which compared oral topotecan plus ASC with ASC alone[7].

Recruitment to study 478, however, did not require patients to be unsuited for anthracycline-based regimens. Moreover, patients were excluded from study 478 if they were deemed unsuitable for intravenous chemotherapy. The assumption of equivalence between intravenous and oral topotecan is based on the results of study 396[10]. It is important to note that the population included in studies 478 and 396 are different in terms of patients' resistance / sensitivity to first-line chemotherapy.

The economic analysis may therefore be based on a population that may be somewhat different from that stated in the decision problem.

The economic analysis considers the resource utilisation and related costs of drug acquisition, drug administration and the management of adverse events attributable to topotecan. EQ-5D scores are obtained from study 478, and are used in the analysis to calculate gains in quality-adjusted life-years (QALYs)[7].

8.3.2 Summary of the key findings

The total, per-patient cost of intravenous topotecan therapy (£5,697) is divided between £3,539 for drug acquisition, £1,660 for drug administration and £498 for the management of adverse events.

The incremental cost per life-year gained of intravenous topotecan plus ASC, relative to ASC alone is £21,302. The corresponding incremental cost per QALY gained is £23,660.

Sensitivity analyses suggested that the cost-utility estimates are robust to variations in input values. The worst case scenario, however, results in an ICER of almost £50,000 per QALY gained. Given that patient-level data are available, it would have been preferable to assess uncertainty by means of a probabilistic analysis.

8.4 Review of evidence on budget impact:

8.4.1 Summary of the evidence

The budget impact analysis detailed in the company submission calculates the expected annual cost of intravenous topotecan therapy[6]. It is assumed in the analysis that costs remain unchanged in each of the next five years. The cost per patient is the same as that described in the economic evaluation, and includes the cost of drug acquisition, administration and management of adverse events.

The incidence of cases eligible for topotecan therapy is calculated as 0.51 per 100,000 of population, equivalent to 15 cases per annum in Wales. The company estimate an uptake of 50%, meaning that 8 patients will receive topotecan annually. However, this analysis excludes 8 potential prevalent cases that might also be initially eligible for topotecan therapy.

8.4.2 Summary of the key findings

The total cost per patient of topotecan therapy is calculated as £5,697 per year. Based on the company submission estimate of 8 patients receiving topotecan annually, and including the costs of administration and management of adverse events, this equals £45,576 per annum.

The company submission included two sensitivity analyses whereby all 15 eligible patients would receive topotecan (at an annual cost of £84,455); and where 25% drug re-use is assumed (at an annual cost of £58,472).

9.0 ADDITIONAL INFORMATION:

9.1 Guidance and audit requirements:

- NICE guidance states that: “second-line chemotherapy should be offered to patients at relapse only if their disease responded to first-line chemotherapy. The benefits are less than those of first-line chemotherapy”[11].
- Topotecan would not be suitable for a shared-care agreement. Treatment initiation, monitoring and supervision should be retained under specialist care.

9.2 Previous AWMSG/NICE advice

National Institute for Health and Clinical Excellence (NICE) clinical guideline 24; “*Lung cancer – The diagnosis and treatment of lung cancer*” February 2005[11]. This guideline predates the availability of toptecan for this indication**.**

9.3 Ongoing studies
None specified[6].

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

The usual approach would be to introduce second-line therapy with a chemotherapy regimen such as a combination of vincristine, adriamycin and cyclophosphamide (VAC). For occasional patients who have had a long initial remission, first-line chemotherapy might be re-introduced usually in the form of cisplatin or carboplatin in combination with etoposide. Unfortunately there is little evidence to support these approaches. Relatively few patients respond and the duration of response is often short. A standard regimen with clear evidence of benefit would be preferable.

It is estimated that that there are 20 cases of SCLC each year of per acute hospital, of which 5 – 7 would be eligible for second-line chemotherapy with topotecan.

There would be a preference to use topotecan as the standard second-line therapy rather than VAC or other regimens if it was available.

9.5 Patient Interest Group
A patient interest group submission by the Roy Castle Lung Cancer Foundation was provided to NMG members.

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Appendix 1. Additional Clinical Information

Definition of resistant patients recruited for Study 478[4]
Patients who had achieved a partial or complete response to first line therapy and progressed at least 45 days after completing first line therapy, who were not candidates for further IV chemotherapy but were considered of sufficient good health to tolerate treatment with single agent oral topotecan.

Definition of sensitive patients recruited for Study 396[4]
Patients who had progressed greater than or equal to 90 days after having a documented response to first line therapy.

Table 1: Study 396 - Definitions for secondary efficacy measures[6]

Time to response: The time from the first dose of study medication to the time of first documented complete or partial response**.**
Response duration: The time from the initial documented response to the first documented sign of progression.
Time to progression (TTP): The time from the first dose of study medication to the time of first documented sign of progression.
Survival: The time from the first dose of study medication to death.
Quality of life: Assessed using the Functional Assessment of Cancer Therapy-G and Lung Cancer Subscale (FACT-L), a 44-item self-reporting instrument consisting of five sections: physical well-being, social/family well-being, emotional well-being, functional well-being, and an index specific to lung cancer and its associated symptoms.

Table 2: Study 478 - Definitions for secondary efficacy measures[6]

Response rate: The percentage of all randomised patients responding to treatment; i.e., patients with complete (CR) or partial response (PR) divided by the total number of patients enrolled.
Time to progression (TTP): The time between randomisation and the first radiologically or clinically documented evidence of progression. All remaining patients who did not progress were censored. This was assessed only for patients receiving oral topotecan plus ASC. A total of 12 patients were censored.
***Control of disease symptoms** (GSK Patient symptom assessment): Patients were asked to assess nine symptoms (shortness of breath, cough, chest pain, coughing up blood, loss of appetite, interference with sleep, hoarseness, fatigue, interference with daily activities) in terms of the degree they had experienced or were bothered by each symptom in the previous three weeks or since the last treatment on a 4-point ordinal scale.
***Quality of life:** Patient utility was assessed by use of the EuroQol (EQ-5D) and Visual Analogue Scale (VAS).

** For all three valuation instruments multiple measurements were taken at regular time intervals during the study*.

Table 3 – Palliative care treatment administered in Study 478[7]

Table 3. Palliative Care Measures

Therapy	Patients			
	BSC (n = 67)		Topotecan (n = 70)	
	No.	%	No.	%
Any medication	55	82	42	60
Pain medication	46	69	33	47
Radiotherapy	17	25	10	14
Transfusions	7	10	23	33
Other procedures	9	13	6	9

NOTE. For all patients who had at least one post–random assignment evaluation in the BSC alone group or one dose of study medication in the topotecan group.
Abbreviation: BSC, best supportive care.

APPENDIX 2. Health Economic Review

Company submission - economic evidence

1. Description and critique of the company submission

The company submission details a cost-effectiveness and cost-utility analysis of intravenous topotecan plus active symptom control (ASC) versus ASC alone, in patients with small cell lung cancer (SCLC) for whom second line chemotherapy is considered suitable, but an anthracycline-based regimen is judged to be inappropriate[6]. The analysis is based on the results of study 478[7], which compared oral topotecan plus ASC with ASC alone. The company assumed therapeutic equivalence of intravenous and oral topotecan based on the findings of study 396[9].

The economic analysis is populated with data on patients' survival and health state utilities taken directly from study 478[7], and healthcare resource utilisation and costs associated with the acquisition and administration of topotecan, and the management of adverse reactions. A lifetime horizon of analysis is adopted, and the results are expressed as incremental costs per life-year, or QALY gained.

2. Population

The company submission describes the economic analysis to represent the use of topotecan in patients who are considered suitable for second-line therapy for SCLC, but where an anthracycline-based regimen is judged to be inappropriate due to pre-existing cardiovascular conditions or contraindications[6]. Recruitment to study 478, however, did not require patients to be unsuited for anthracycline-based regimens. Moreover, patients were excluded from study 478 if they were deemed unsuitable for intravenous chemotherapy. Reasons for unsuitability included patients' personal choice, a very short time to progression (<90 days) following first-line chemotherapy and short time to progression plus residual toxicity from first-line chemotherapy.

The assumption of equivalence between intravenous and oral topotecan is based on the results of study 396[9]. It is important to note that the population included in studies 478 and 396 are different in terms of patients' resistance / sensitivity to first-line chemotherapy.

The economic analysis may therefore be based on a population that may be somewhat different from that stated in the decision problem.

3. Perspective and time horizon

The economic analysis considers healthcare resource utilitisation and costs from the perspective of the NHS in Wales. Personal and social service costs /resources are not considered explicitly.

A life-time horizon of analysis is adopted.

4. Comparator

In the absence of identifiable alternative non anthracycline-based regimens for second-line chemotherapy for SCLC[9], active symptom control (ASC) is deemed appropriate. Although the company submission does not provide details of what constitutes ASC, study 478 described ASC as encompassing palliation and support modalities with which patients who are not candidates for further polychemotherapy are treated. For example, ASC would include the use of medications (including

analgesics for pain, antibiotics for intercurrent infections, steroids, appetite stimulants and antidepressants) as well as the use of procedures such as radiotherapy to specific troublesome sites of disease, transfusion support for anaemia, the use of deep relaxation therapy and palliative surgical procedures such as the drainage of effusions. ASC excludes therapies which could specifically inhibit tumour cell growth or spread, such as chemotherapy or cytokine therapy.

5. Clinical inputs

5.1 Efficacy

The efficacy of intravenous topotecan is based on study 478; details of which are reported in section 6 of the appraisal report. The primary endpoint of study 478 is overall survival. Median survival time in patients receiving topotecan plus ASC is 25.9 weeks (95% CI 18.3, 31.6), compared with 13.9 weeks (95% CI 11.1, 18.6) in patients receiving ASC alone (log-rank p=0.0104). The unadjusted hazard ratio for oral topotecan plus ASC versus ASC alone is 0.638 (95% CI: 0.45, 0.90). At the end of the 184-week follow-up period, fewer than 5% of patients were alive in the topotecan arm, while all patients had died in the ASC arm.

5.2 Health outcomes

The mean undiscounted life-years gained, determined from analysis of mean survival (area under the Kaplan-Meier survival curve), is presented as 0.752 and 0.485 for the topotecan plus ASC, and ASC alone treatment groups, respectively.

EQ-5D scores obtained from study 478, are used in the analysis to calculate gains in quality-adjusted life-years (QALYs) [7]. For both groups of the trial, weighted mean EQ-5D scores are calculated, by considering the product of the mean utility value at a given point in time, and the number of patients alive at that point. As EQ-5D scores were only measured for the first 36 weeks in study 478, and 35% of patients receiving topotecan plus ASC and 20% of patients receiving ASC alone survived beyond 36 weeks, it is assumed in the company submission that the weighted mean utility up to 36 weeks is representative of overall utility.

The mean utility scores for patients treated with topotecan plus ASC is calculated as 0.691, compared with 0.561 for patients receiving ASC alone.

It is more conventional in economic analyses conducted alongside randomised controlled trials, to calculate the overall utility of individual patients, and conduct a bootstrapping analysis (or an appropriate alternative) to determine the mean effect. It is unclear whether the estimates provided are likely to differ substantially had an alternative method of analysis been conducted.

5.3 Adverse events

The company submission included the healthcare resources required to manage the following adverse events that are associated with topotecan therapy: sepsis, febrile neutropenia, vomiting, diarrhoea, and anaemia[6]. The incidence of adverse events attributable to topotecan is calculated as the difference in incidence between both treatment groups of study 478[7]. Certain haematological adverse events (e.g. leucopoenia and thrombocytopenia) are not considered in the economic analysis, although it is acknowledged that thrombocytopenia is managed, in practice, by dose-adjustment.

6. Healthcare resource utilisation and cost

The economic analysis considers the resource utilisation and related costs of drug acquisition, drug administration and the management of adverse events attributable to topotecan.

The cost of topotecan 1mg and 4mg vials is £97.65 and £290.62, respectively[8]. The overall cost of drug is based on a calculation of the mean administered dose of 1.39 mg/m^2/day (taken from study 396), mean body surface area of 1.85 m^2 (study 478) and 3.79 cycles per patient (study 478). Drug wastage is not considered in the base-case analysis, but is included in the sensitivity analysis.

The cost of treatment administration is based on the first of the five contacts per cycle of topotecan therapy being made with a physician, and the remainder by a nurse. The costs of administration are based on hourly employment rates; added to which is the cost of blood tests, required as part of topotecan therapy.

As patients receiving topotecan and those in the comparator group all receive ASC, the cost of ASC is excluded from the analysis. However, it is unclear whether this is entirely valid, as the intensity and duration of ASC is unlikely to be equivalent in patients receiving topotecan, versus those who do not.

The overall mean cost per patient of managing adverse events (AEs) is calculated as the sum-product of the unit costs and the incidence of AEs due to topotecan. Costs included: 13 days admission to intensive care unit for the management of sepsis; inpatient treatment for febrile neutropenia (it is unclear whether or not this includes the cost of G-CSF); the cost of red blood cell transfusion for correction of anaemia; and the costs of pharmacological management of vomiting and diarrhoea.

7. Discounting

All costs are assumed to occur within the first year, and are therefore not discounted. As some patients' survival exceeds one year, health outcomes are discounted at the recommended annual rate of 3.5%.

8. Results

8.1 Base-case

The total per-patient cost of intravenous topotecan therapy is divided between £3,539 for drug acquisition, £1,660 for drug administration and £498 for the management of adverse events.

The incremental cost per life-year gained of intravenous topotecan plus ASC, relative to ASC is £21,302. The corresponding incremental cost per QALY gained is £23,660.

Table one: Incremental cost per QALY

	Total cost	Life-years gained	QALYs	Incremental cost per LYG	Incremental cost per QALY
Topotecan plus ASC	£5,697	0.752	0.510	£21,302	£23,660
ASC	£0	0.485	0.269		

8.2 Sub-group analysis
No sub-group analyses are considered in the evaluation.

9. Sensitivity analysis
The results of extensive univariate and bivariate sensitivity analyses are presented. They include assumptions relating to drug wastage, discount rate, health state utility scores, the costs of managing adverse events, assumptions relating to survival benefits, and the costs of drug administration. The results of the univariate analyses are summarised in the table below.

Table two : Univariate analyses for topotecan treatment of SCLC

Variable	Optimistic estimate	Pessimistic estimate
Drug wastage	No wastage £23,660	No re-use £32,584
Discount rate	0% £22,968	3.5% £23,660
Health state utility	Adjustment of utility values in ASC group (weeks 21 to 36) £23,118	Utility score in topotecan group reduced by 50% £29,549
Costs of managing adverse events	Incidence of AEs halved £22,625	Incidence of AEs doubled £25,730
Survival benefits	10% more survival with topotecan £19,527	10% less survival with topotecan £30,012
Costs of drug administration	Base-case £23,660	Doubling of administration costs £30,553
Multivariate analysis (best and worst case scenarios)	Vial wastage included (75% re-use); 10% more survival; 50% increase in utility £18,095	Vial wastage included (25% re-use); 10% less survival; 50% decrease in utility £49,841

Incremental cost-utility estimates are maintained within the approximate £20-30,000 per QALY range under the different scenarios, though the selection of ranges is arbitrary in some cases (e.g. survival benefits). The worst case scenario, however, is close to £50,000 per QALY gained. Given that data are available for individuals, a more robust analysis of uncertainty (e.g. a probabilistic sensitivity analysis) would be preferred.

Company submission - budget impact analysis

1. Description and critique of the company submission

The budget impact analysis detailed in the company submission calculates the expected annual cost of intravenous topotecan therapy[6]. It is assumed in the analysis that the cost remains unchanged in each of the next five years. The cost per patient is the same as that described in the economic evaluation, and includes the cost of drug acquisition and administration, and of managing adverse events.

2. Perspective and time horizon

The perspective adopted in the budget impact analysis is that of the NHS in Wales, with a one-year time horizon (costs assumed to be the same in each year).

3. Data sources

3.1 Incident cases

The number of incident SCLC cases in Wales, who are eligible to receive second-line chemotherapy, but who cannot be prescribed anthracycline-based regimen, is estimated by multiplying the following annual figures:

a) the incidence of lung cancer (estimated at 0.0763%) – slightly higher than the 2005 values presented by the Welsh Cancer Intelligence & Surveillance Unit[12]
b) the percentage of lung cancer patients having SCLC (20%)
c) the percentage of SCLC patients having 1st line therapy (67%)
d) the percentage of patients eligible to receive second line chemotherapy (50%)
e) the percentage of patients eligible for non anthracycline-based 2nd line therapy (10%)

The resulting incidence of cases eligible for topotecan therapy is thus calculated as 0.51 per 100,000 of population, equivalent to 15 cases per annum in Wales.

3.2 Prevalent cases

The company submission did not consider prevalent cases.

Given that prevalence equals incidence multiplied by mean duration of disease, and based on the figures provided (mean duration of disease in ASC group of study 478 is approximately 6 months; annual incident cases in Wales is 15), the number of prevalent cases is approximately 8.

3.3 Market share

The company estimate an uptake of 50%, meaning that 8 patients will receive topotecan annually.

3.4 Rates of adoption

The company did not consider differential rates of adoption.

3.5 Displaced medicine(s)

The company did not consider any displaced therapy as topotecan is unlikely to displace any current therapy.

4. Results

4.1 Base-case

The total cost per patient of topotecan therapy is calculated as £5,697 per year. Based on the company submission estimate of 8 patients receiving topotecan annually,and including the costs of administration and management of adverse events, this equals £45,576 per annum.

4.2 Sub-group analysis

The company did not conduct any sub-group analyses.

5. Sensitivity analysis

The company submission included two analyses whereby all 15 eligible patients would receive topotecan (at an annual cost of £84,455); and where 25% drug re-use is assumed (at an annual cost of £58,472).