topotecan 0.25mg, 1mg hard capsules (Hycamtin®) No. (545/09) GlaxoSmithKline

06 March 2009

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

topotecan capsules (Hycamtin®) are accepted for restricted use within NHS Scotland as monotherapy for the treatment of adult patients with relapsed small cell lung cancer (SCLC) for whom re-treatment with the first-line regimen is not considered appropriate.

The efficacy of topotecan capsules relative to standard IV chemotherapy is unknown. Topotecan capsules are restricted to use in patients for whom standard intravenous chemotherapy is inappropriate and who would otherwise receive best supportive care.

In one study, oral topotecan plus best supportive care (BSC) was superior to BSC alone for the primary endpoint of median survival.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

As monotherapy for the treatment of adult patients with relapsed small cell lung cancer (SCLC) for whom re-treatment with the first-line regimen is not considered appropriate.

Dosing information

Topotecan 2.3mg/m^2 body surface area/day administered for 5 consecutive days with a 3-week interval between the start of each course. If well tolerated, treatment may continue until disease progression.

Topotecan capsules should only be prescribed, and therapy supervised, by a physician experienced in the use of chemotherapeutic agents.

Product availability date

26 September 2008

Summary of evidence on comparative efficacy

Topotecan is a cytotoxic anti-cancer agent which exerts its activity by the inhibition of the nuclear enzyme topoisomerase I. Topotecan infusion has been available for the treatment of small cell lung cancer (SCLC) since January 2006. In this submission the company has requested that SMC consider the use of topotecan capsules in patients with relapsed SCLC who are not considered candidates for standard intravenous therapy with cyclophosphamide, doxorubicin and vincristine (CAV) chemotherapy regimen (i.e. patients who have contraindications to components of the CAV regimen or those for whom intravenous therapy access is difficult or refused), and for whom best supportive care is currently the only option.

Two phase III open-label studies have investigated the use of oral topotecan for the treatment of relapsed SCLC. Patients were eligible if they were ≥18 years, had received one prior chemotherapy regimen only, and had documented partial or complete response to first-line therapy and an Eastern Co-operative Study Group (ECOG) performance status (PS) score of ≤2. Patients were also required to have documented relapse of limited or extensive SCLC at least 45 and 90 days after cessation of first-line chemotherapy in the first and second trials respectively.

The first study recruited 141 patients who were not considered suitable for further intravenous chemotherapy to receive either best supportive care (BSC) alone or BSC plus oral topotecan 2.3mg/m^2/day for 5 consecutive days repeated every 21 days. BSC encompassed all palliation and support modalities (including analgesics, antibiotics, corticosteroids, antidepressants, transfusions for anaemia, deep relaxation therapy, palliative radiotherapy or surgical procedures). The primary study objective was overall survival, defined as time from randomisation until death from any cause and secondary objectives included response rate, time to disease progression (TTP) and quality of life (measured using the EuroQOL-5 Dimension Health Questionnaire [EQ-5D], an evaluation of five health status dimensions). A total sample size of 220 patients was required to assess a survival benefit for topotecan with 90% power, at the 0.05 significance level. However, due to slow patient recruitment the protocol was amended to terminate the trial at 125 deaths, which provided 80% power at the 0.05 significance level.

The intention-to-treat (ITT) population (all randomised patients) comprised 71 and 70 patients in the oral topotecan plus BSC and BSC alone groups, respectively. The median

survival in the oral topotecan plus BSC group was 25.9 weeks compared to 13.9 weeks in the BSC alone group (unadjusted hazard ratio [HR] for oral topotecan plus BSC relative to BSC alone 0.64, 95% confidence interval [CI]: 0.45 to 0.90). In sub-group analysis median survival was longer in the topotecan plus BSC arm than for BSC alone both in patients with and those without liver metastases, although the difference was not significant for the former sub-group. Furthermore, median survival was longer for the topotecan plus BSC group than for BSC alone both for patients with a time to progression following first-line chemotherapy of >60 days and ≤60 days, although the differences in both sub-groups were not significant.

In the oral topotecan plus BSC arm five patients (7.0%) had a partial response to treatment and no patients had a complete response. The median TTP for the oral topotecan plus BSC group was 16.3 weeks (95% CI: 12.9 to 20.0) and was not reported in the BSC alone group. The rate of change over 3 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 BSC and BSC alone groups respectively.

The second study was designed to investigate the clinical profile of intravenous (iv) topotecan (1.5mg/m^2 intravenous infusion for 5 consecutive days every 21 days) with topotecan oral (dosing regimen as in the first study) as second-line therapy in patients with advanced SCLC. The primary objective of the study was to demonstrate non-inferiority of oral to iv topotecan with respect to response (partial or complete) rate. Secondary objectives included survival and quality of life (assessed using the Functional Assessment of Cancer Therapy-G and Lung Cancer Subscale [FACT-L] which consists of five health status dimensions including an index specific to lung cancer and its symptoms). The ITT population comprised 153 and 151 patients in the topotecan oral and topotecan iv groups respectively. A total of 28 patients (18%) responded to treatment with oral topotecan versus 33 patients (22%) in the iv topotecan group. The percentage difference (oral minus iv) was -3.6% (95% CI: -12.6% to 5.5%). At the lower non-inferiority bound of -10%, non-inferiority of oral topotecan to iv topotecan was not demonstrated for response rate. The median survival for topotecan oral was 33 weeks compared with 35 weeks for topotecan iv (HR 0.95; 95% CI: 0.75 to 1.21). In terms of quality of life, there was no significant difference between oral and iv treatments in change from baseline in total FACT-L scores.

Summary of evidence on comparative safety

The European Medicines Agency (EMEA) notes that there are no new safety issues for topotecan when used in relapsed SCLC as compared with relapsed ovarian cancer. In addition, no major differences regarding safety risks were found between iv and oral topotecan. The principal adverse events associated with topotecan in relapsed SCLC related to bone marrow suppression.

In the first study more patients in the topotecan plus BSC arm compared with BSC alone arm had grade 3/4 neutropenia (61% versus 11%), leucopenia (41% versus 0%), thrombocytopenia (38% versus 4.3%) and anaemia (25% versus 6.4%).

In the study comparing iv topotecan to oral topotecan the incidence of haematological toxicity, especially grade 3/4 neutropenia, for iv topotecan was higher when compared to oral topotecan (88% versus 73%). However infectious complications, sepsis and drug related mortality were similar in the two arms.

Summary of clinical effectiveness issues

Topotecan is the only oral chemotherapy regimen licensed for use in relapsed SCLC. There are, however, no controlled studies comparing oral topotecan with comparator chemotherapy regimens other than with iv topotecan. The company has suggested that oral topotecan should be used in patients who are not considered candidates for standard iv therapy with CAV, and for whom BSC is currently the only option. In this setting BSC is therefore the most appropriate comparator.

In the first study, patients were eligible if they were considered unsuitable for further iv chemotherapy. Unsuitability was based on local policy concerning unproven risk and benefit in patients with resistant (i.e. a short treatment-free interval) SCLC and assessed on an individual basis. Reasons why a patient was not considered a candidate for further iv chemotherapy were not captured fully for the trial. However, potential reasons included a very short TTP following an initial response to first-line chemotherapy, a relatively short TTP from, and residual toxicity to, first-line chemotherapy, and patient preference. Also in this study, the power to detect a difference in overall survival was reduced to 80% following a protocol amendment due to slow patient accrual.

The use of oral topotecan in patients for whom standard intravenous chemotherapy is inappropriate, for example due to contra-indications to anthracyclines, will allow a treatment option for patients who would otherwise receive BSC alone. Clinical experts consulted by SMC have advised that the treatment will offer clinical benefits in this patient population.

Summary of comparative health economic evidence

The manufacturer provided a lifetime cost-utility analysis using patient-level data comparing oral topotecan to BSC in adult patients with relapsed SCLC. The manufacturer acknowledged that CAV is a key treatment for patients with relapsed SCLC who can tolerate further chemotherapy and for whom re-treatment with the first-line regimen is not considered appropriate (i.e. the licensed indication for topotecan) but they recognised that topotecan would not provide a cost-effective alternative to CAV in the majority of patients given its relatively high acquisition cost. As such, they have chosen to niche the submission to an area where treatment with oral topotecan may be more cost-effective i.e. patients with relapsed SCLC not considered as candidates for standard iv therapy and who would otherwise receive BSC.

Directly comparative clinical study data were available for the comparison of interest, which was helpful but it should be noted that the trial was small and was open-label. The study had uncensored data on the vast majority of patients and for the six patients (three in each arm) for whom data were censored (because they were still alive at the final follow-up) it was assumed that the patients died at that point. EQ-5D data were collected in the study, which aided the cost-utility analysis modelling. However there was a large amount of missing data in the data set. Complete resource use information was not collected in the study and therefore resource use estimation was supplemented using information collected from a survey of five UK clinicians. Resource use and costing was generally well-described and covered resource use associated with the adverse event profile of topotecan.

The results showed an incremental cost of £5,671 per patient and a gain in Quality Adjusted Life Years (QALYs) of 0.211 to give a cost per QALY ratio of £26,833. One-way sensitivity

analysis showed that the Incremental Cost Effectiveness Ratio (ICER) rose to over £30,000 if the assumptions made on quality of life values, drug administration costs, or costs associated with adverse events were changed.

Sensitivity analysis also showed lower cost effectiveness ratios in certain subgroups; women, patients without liver metastases, and patients with a time to progression of ≤60 days following previous therapy. However these findings were based on small patient numbers and thus should be viewed with caution. Probabilistic sensitivity analysis indicated a 60% probability that topotecan would be cost-effective at a willingness to pay of £30,000.

There were a number of issues with the analysis:

- There were large amounts of missing data in the EQ-5D data set, which could introduce bias into the results, and additionally the results were sensitive to the general methods used to derive the utility scores from the EQ-5D data. However additional sensitivity analysis was provided to show that some of the methods used to derive the utility gains in the base case were, in fact, conservative.
- No sensitivity analysis was initially available to test the assumptions on how survival in censored patients had been handled. Analysis has subsequently been provided to show that even if a pessimistic assumption was made that censored BSC patients survived for a year longer than the censored topotecan patients, the ICER remained just below £30,000 per QALY.
- Some differences were noted between this oral topotecan submission and the iv topotecan submission to SMC in 2007, such as Life Year (LY) gain, QALY gain, and adverse event costs, despite both submissions using the same trial data. The manufacturer's response indicated that the different ICERs were largely due to the analyses being carried out by two different economic modellers and suggested that the current analysis using individual patient level data was the more robust approach.

Despite these concerns, the economic case was considered adequately demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network published guideline 80; *Management of patients with lung cancer* in February 2005. The guideline states; "second-line chemotherapy in patients with SCLC should be considered depending on the duration of response to first-line chemotherapy and on patients' performance status and wishes". The need for an update for this guideline is currently being considered.

The National Institute for Health and Clinical Excellence (NICE) published guideline number 24, entitled; *The diagnosis and treatment of lung cancer,* in February 2005. It states, "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".

Both guidelines predate the availability of topotecan for the indication under review.

NICE is undertaking a Multiple Technology Assessment of topotecan for the second-line treatment of SCLC and publication is expected in November 2009.

Additional information: comparators

Intravenous topotecan (not accepted for use by SMC for relapsed SCLC) and the CAV chemotherapy regimen (cyclophosphamide, doxorubicin, vincristine) are potential second-line treatments for relapsed SCLC. In this submission the company are proposing the use of oral topotecan in patients who are not considered candidates for standard iv therapy with CAV, and for whom BSC is currently the only option.

Cost of relevant comparators

Drug	Dose regimen	Cost per cycle (£)	Cost per course (4 cycles) (£)
Topotecan	**topotecan 2.3 mg/m^2 orally on days 1 to 5, every 21 days**	**600**	**2400**
Topotecan	topotecan 1.5mg/m^2 IV on days 1 to 5, every 21 days	1453	5812
CAV	cyclophosphamide 1 g/m^2, doxorubicin 45 mg/m^2, vincristine 2mg IV on day 1, every 21 days	195	780

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF no. 56 (September 2008) and MIMs (12/08) for topotecan capsules. Costs based on a body surface area of 1.7m^2 and have assumed wastage of remaining contents of vials. Cost per course includes 4 cycles based on median number of cycles given in pivotal trials. Topotecan IV for this indication is not recommended by SMC.

Additional information: budget impact

If used within the patient population proposed, the manufacturer estimated a budget impact of £163k in year one rising to £187k in year five. These costs were estimated from the overall health service costs in the economic model to include drug acquisition, administration, monitoring and adverse event costs; direct drug costs only were 44% of these costs. Thirty patients were assumed to be eligible and treated with topotecan in year one rising to 34 patients by year five, representing an estimated 16% of the total number of patients who are eligible to be given a second-line treatment. It should be noted that SMC experts have raised the potential for greater usage than suggested by the manufacturer's figures, particularly if used in a wider patient population than is covered by this advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 13 February 2009.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

O'Brien M, Ciuleanu T, Tsekov H, *et al*. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol 2006; 24(34): 5441-5447

Eckardt J, von Pawel J, Pujol J, *et al*. Phase III study of oral compared with intravenous topotecan as second line therapy in small-cell lung cancer. J Clin Oncol 2007; 25(15): 2086-2092

von Pawel J, Schiller J, Shepherd F, *et al*. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol 1999; 17(2):658-667

The European Medicines Agency (EMEA) European Public Assessment Report. Topotecan (Hycamtin ®). 6/01/2006, EMEA H/C/123/II/34. www.emea.europa.eu