Appendix C
Summary form

National Institute for Health and Clinical Excellence

Topotecan for the second-line treatment of small cell lung cancer

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	GSK	We consider that it is appropriate to refer this topic to NICE for appraisal	Noted
	Roy castle lung foundation	Yes. Past history shows that new anti-cancer products which are not appraised by NICE, have little chance of being approved for NHS use.	Noted
Wording	GSK	Since the likely indication for topotecan will be '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' we suggest that the remit is re-worded slightly to reflect this qualification.	This is now reflected in the scope under population
Timing Issues	GSK	CHMP positive opinion for the oral Hycamtin marketing authorisation was received on 24 Jan 2008 and the Commission Decision is expected on or around 30 March 2008. Although there does not appear to be any suggested timing for submission of evidence on the cover letter, we believe it is appropriate for topotecan for relapsed small cell lung cancer (SCLC) to be appraised as part of the 17th Wave.	Noted
	Roy castle lung foundation	Very urgent. As noted in your Scope, the prognosis for this patient group is extremely poor.	Noted
Additional comments on the draft remit	GSK	None	

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	GSK	We suggest that the epidemiology within the background section is updated with recent data from the National Lung Cancer audit (1). e.g. the report estimates that there were 33,000 lung cancer cases in England and Wales in 2006. Ten percent of these cancers were small cell carcinomas, or about 3,300 new cases per year. This steep reduction in incidence in SCLC may possibly be due to changing smoking habits and a reduction in the tar content of cigarettes (2). We believe that the place of radiotherapy in the treatment of lung cancer should be clarified. Whilst we agree that radiotherapy has an important role to play, its use tends to be as part of the total first line treatment protocol, if there has been a complete response at distant sites and at least a good partial response within the thorax (3). Radiotherapy in this setting is used either concurrently with first line chemotherapy, or afterwards, as part of the first line protocol. For completeness, it may be useful to add that prophylactic cranial irradiation should be considered for patients with limited disease and complete or good partial response after primary treatment (3). This is not generally considered as a second line treatment. 1. The Information Centre for Health and Social care. (2007) 'National Lung Cancer Audit, key findings about the quality of care for people with Lung Cancer in England and Wales, Report for the audit period 2006'. Leeds, NHS. www.ic.nhs.uk 2. Govindan R., Page N., Morgensztern D et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic and end results database. Journal of Clinical Oncology (2006) Vol. 24 (26): 4539-4544 3. National Institute for Clinical Excellence (February 2005). 'Diagnosis and treatment of lung cancer'. National Collaborating Centre for Acute Care, London. Available from www.rcseng.ac.uk	Background section now updated to include suggestions where appropriate

Section	Consultees	Comments	Action
	DOH	(Paragraph 2, lines 3-5): In our opinion, the figures presented here are historical. The proportion of lung cancer cases of small cell type has been steadily falling, and in the recent report of the National Lung Cancer Audit (December 2007 – http://www.ic.nhs.uk/our-services/improving-patient-care/more-about-the-audits/audit-reports/lung), that proportion was only 10%. We feel that this is an underestimate resulting from incomplete data collection, and that it is likely to be around 12%. In absolute terms, the predicted numbers at present in England and Wales is around 3000. Also in the National Lung Cancer Audit, the proportion of cases with limited stage disease was 24%, with the rest having extensive disease. (Paragraph 2, lines 8-10); In our opinion, the statement on the limited value of TNM staging is now outdated. The recent report from the International Association for the Study of Lung Cancer (IASLC) to the UICC staging body is that TNM staging in SCLC is a good indicator of outcome, and that it should now be adopted as the staging method for SCLC (this staging system will come into force in early 2009). Could you please consider the factoring of these recent data into any proposed analyses.	Comments incorporated into the updated scope
The technology/ intervention	GSK	This section should be updated with details of the regulatory status of topotecan in SCLC: The CHMP recently issued a positive opinion for oral topotecan in the SCLC indication. The marketing authorisation is expected by the end of March 2008.	Scope now updated to reflect regulatory status of topotecan
Population	GSK	We suggest that the wording be amended slightly to reflect the licensed population for topotecan in small cell lung cancer (both oral and intravenous (IV)): 'Adult patients with small cell lung cancer that has relapsed following previous therapy and for whom re-treatment with the first-line regimen is not considered appropriate'. Within the licensed population, there are two subgroups that we believe are of particular interest, and should be considered separately: For oral topotecan: patients for whom an IV chemotherapy is unsuitable For both oral and IV topotecan: patients with serious pre-existing cardiovascular conditions, for whom treatment with an anthracycline-based regimen would not be clinically appropriate.	Scope has been updated to reflect the licensed population

Section	Consultees	Comments	Action
	DOH	In view of the relatively small number of suitable patients, could you please consider the inclusion of some form of cost impact analysis in the brief. There appears to be no mention in the document of the proportion of SCLC patients, who might be suitable for second line chemotherapy. In our view, expert opinion, published and audit data should be sought, in order to try and establish this. In terms of the indication for second line treatment in SCLC, there is a general professional view that patients, who relapse after first line treatment (perhaps within thee months), have a worse prognosis than those who relapse later. We feel that opinion needs to be sought as to whether a different approach to second line treatment needs to be considered, in these two groups of patients.	The scope template does not require including cost impact analysis. This will be presented in the actual submissions and assessment group reports. Most of the issues raised here will be dealt with in the actual appraisal process.

Section	Consultees	Comments	Action
Comparators	GSK	In relation to the question of which chemotherapy regimens are most commonly used in current clinical practice for the subsequent treatment of people who have relapsed after a complete or partial response to first-line therapy, audit data, market research and clinician opinion suggest the following: Sixty percent of patients receive active treatment as their first line therapy for SCLC; 10% of patients receive specialist palliative care and 24% are classed as receiving 'no specific anti cancer treatment' (1). Approximately 85% of patients with extensive disease and more than 90% of those with limited disease respond to initial therapy, but nearly all of these patients will relapse, usually within a year (2). Approximately three quarters of patients that relapse receive best supportive care (3, 4). Of the remaining 25% that do receive a second line chemotherapy, around 40% receive CAV, 15% receive platinum plus etoposide, and 15% receive IV topotecan monotherapy (3). Since 75% of patients who relapse do not receive active treatment, we strongly believe that best supportive care should be considered as the key comparator in this appraisal. CAV is the treatment of choice in the majority of patients who receive a second line chemotherapy, and therefore should be considered as a relevant comparator in patients for whom IV chemotherapy is appropriate. Topotecan is indicated for the treatment of patients with relapsed SCLC for whom retreatment with their first line regimen is not considered appropriate. Since platinum drugs and etoposide are first line regimens, and their use in the second line setting tends to be as retreatments, we believe that these regimens are not valid comparators. IV topotecan is used in a minority of patients and as such we believe that it should not be considered as a standard comparator. As mentioned above, radiotherapy has an important role to play, but its use tends to be as part of the total first line treatment protocol. Therefore we believe that radiotherapy is not a relevant comparator in relapsed disease. In summary, we believe that relevant comparators in this appraisal are: - Best supportive care - CAV (1) The Information Centre for Health and Social Care. (2007) 'National Lung Cancer Audit, Key findings about the quality of care for people with Lung Cancer in England and Wales, Report for the audit period 2006'. Leeds, NHS. www.ic.nhs.uk (2) Decision Resources (January 2003). Pharmacor - Small-Cell Lung Cancer (3) GlaxoSmithKline Market Research, July 2006 (4) UK Key Opinion Leader feedback, November to December 2007.	Comparators have been updated in the latest scope to reflect the suggestions here.

Section	Consultees	Comments	Action
	Roy castle lung foundation	Also, comparator with no other active anti-cancer treatment.	As above
Outcomes	GSK	We are comfortable that the suggested outcomes capture many of the important health related benefits, but suggest the addition of the following important secondary endpoints: Time to progression Proportion of patients with stable disease Time to response Symptom scores	Agreed by NICE team that the main standard outcomes will remain and the manufacturer could present additional outcomes. Time to progression and symptom control have been added to the outcomes in the scope.
	DOH	Could you please consider another outcome measure, ie, symptom control (not identical to Quality of Life, although it is included in most QOL scales).	Symptom control has been added to the outcomes in the scope.
	Roy castle lung foundation	Symptom control and quality of life are extremely important in this patient population. This should be reflected in considering the outcome measures.	Symptom control has been added to the outcomes in the scope.
Economic analysis	GSK	The scope for the economic analysis is reasonable and we have no specific comments.	Noted
Other considerations	GSK	None	Noted

Section	Consultees	Comments	Action
Questions for consultation	GSK	In answer to those questions for consultation not answered above: We believe that the proposal to appraise topotecan through the STA process is appropriate. It is reasonable to suggest that the oral and intravenous formulations be addressed in the same appraisal, and we would welcome the opportunity to discuss this further at the scoping meeting. Regarding groups in which topotecan is expected to be particularly clinically or cost effective, sub-groups from the pivotal clinical trial supporting oral topotecan versus best supportive care (study 478) were stratified on the basis of gender, time to progression from prior therapy (<=60 days or >60 days), performance status (0/1 or 2/3/4), and the presence of liver metastases. Subgroup analyses indicate that prolongation of survival in the topotecan group was preserved in the sub groups, and that topotecan may provide particular benefits in women, those with performance status of 2-4, and those with a shorter time to progression from prior therapy.	Subgroups will be explored whenever there is the relevant data to do so.
	Roy castle lung foundation	In answer to question 3, yes - both oral and iv should be considered.	Noted
Additional comments on the draft scope.	GSK	None	
Comments on matrix of consultees & commentators	GSK	MerckSerono should be removed from the provisional matrix as they no longer have a commercial interest in topotecan.	Merck Serono has been removed from the manufacturer section of the matrix.

Comment 4: Regulatory issues

Section	Consultees	Comments	Action
Remit	GSK	Please see above comment regarding remit	
Current or proposed marketing authorisation	GSK	Topotecan IV monotherapy is indicated for the treatment of: patients with metastatic carcinoma of the ovary after failure of first-line or subsequent therapy. patients with relapsed small cell lung cancer (SCLC) for whom re-treatment with the first-line regimen is not considered appropriate. IV Topotecan 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.	Noted
		Oral topotecan will be indicated 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. [redacted]	Noted
		Oral topotecan monotherapy in relapsed SCLC : Submission made in May 2007. [redacted]	Noted
		Centralised procedure	
		Oral topotecan monotherapy in relapsed SCLC : CHMP opinion on 24/01/08, commission decision (ie regulatory approval) expected around 30/03/08. [redacted]	Noted
		Please note that the above information regarding future marketing authorisations and indications may only be made available to the public after the Commission Decisions.	Noted

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

1. Department of Health
2. Diabetes UK
3. Royal College of Physicians (endorse comments by British Association of Dermatologists
4. Welsh Assembly Government
5. Institute of Physics & Engineering in Medicine
6. NHS Quality Improvement Scotland