National Institute for Health and Clinical Excellence

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

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	GlaxoSmithKline (GSK)	We agree that it is appropriate to refer this topic to NICE for appraisal.	Comment noted. It was agreed at the scoping workshop that an appraisal of topotecan was appropriate.
	Royal College of Nursing (RCN)	Yes this is an appropriate topic to be referred to NICE	Comment noted. It was agreed at the scoping workshop that an appraisal of topotecan was appropriate.
	Royal College of Pathologists (RCPath)	Yes	Comment noted. It was agreed at the scoping workshop that an appraisal of topotecan was appropriate.
	Royal College of Physicians (RCP)	Yes; currently no guidance but this is a small and diverse clinical group of patients. A 'one fits all' approach is difficult. cispltatin and topotecan represents the only significant RCT for recurrent/stage IV cervix cancer but it has not been compared against best supportive care (BSC). Thus, BSC cannot be considered as the standard comparator. There have been 15 other RCTs, most comparing cisplatin with combination therapies. Several have shown improved relative risk (RR) but none apart from cis-topotecan showed a survival benefit. The cis-topo trial was done in a mixed group of women - many had not received prior platinum with radiation. Now virtually all patients with recurrent disease who are being considered for platinum based chemotherapy will have received platinum as part of chemoradiation. This raises the question of the applicablity of the results to a 2008 population, and how to give guidance to the significant group in whom cisplatin-topotecan cannot be considered appropriate.	It was agreed at the scoping workshop that BSC was not an appropriate comparator. This has been amended in the scope It was agreed at the scoping workshop that patients should be considered in groups according to their prior exposure to platinum based chemotherapies. This has been amended in the scope.

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	Cochrane Gynaecological Cancer Review Group	Fine	Comment noted. It was agreed at the scoping workshop that an appraisal of topotecan was appropriate.
	Rarer cancers forum	It is very appropriate as despite screening programmes it is second only to breast cancer in malignant disease among women and indeed many of these women are the most disadvantged in our society	Comment noted. It was agreed at the scoping workshop that an appraisal of topotecan was appropriate.
Wording	GSK	The wording of the remit of this appraisal is reasonable; we have no specific comments.	Comment noted, no action required.
	RCN	We agree with the wording of the scope. It reflects the issues about clinical and cost effectiveness for this health technology.	Comment noted, no action required.
	RCPath	No comment	Comment noted, no action required.
	RCP	The trial of topotecan/cisplatin compares the addition of topo to cis, not a comparison with BSC. Currently patients receive a vairety of treatments, including chemotherapy with eg taxanes, gemcitabine-based on phase II data, or BSC. To consider only non chemotherapeutic alternatives as the standard comparator is wrong but this creates a difficulty for NICE as drugs are used outside license as other manufacuters of drugs have not undertaken licensing trials	It was agreed at the scoping workshop that the comparators should include platinum based mono and combination therapies. This has been amended in the scope NICE does not require comparator drugs to be used within their marketing authorisation if they are being used as part of standard care.
	Cochrane Gynaecological Cancer Review Group	OK	Comment noted, no action required.

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	Rarer cancers forum	We are as ever concerned that the model of any comparison such as best supportive care are open for us all to see and judge	It was agreed at the scoping workshop that BSC was not an appropriate comparator. This has been amended in the scope.
Timing Issues	GSK	In view of the availability of clinical guidelines (e.g. SIGN) and current national (SMC and AWMSG) guidance for the treatment of cervical cancer, we consider that there may be other technologies of higher priority for appraisal.	Comment noted. Following the final referral from the Department of Health, the appraisal will be planned into the technology appraisal schedule to allow as timely as possible guidance to the NHS.
	RCPath	No comment	Comment noted, no action required
	RCP	These tumours should be treated in designated centres. If this combination of treatment - the only licenced one is being refused by PCTs in these centres, then there is an urgency for NICE to step in. If this is not the case, and PCTs accept that centres have the clinical expertise to make judgements about when to use drugs licensed for an indication, or other treatments, then there is less urgency	Comment noted. Following the final referral from the Department of Health, the appraisal will be planned into the technology appraisal schedule to allow as timely as possible guidance to the NHS.
	Cochrane Gynaecological Cancer Review Group	Needs appraisal now	Comment noted. Following the final referral from the Department of Health, the appraisal will be planned into the technology appraisal schedule to allow as timely as possible guidance to the NHS.
	Rarer cancers forum	As women are dying from this disease we need this now	Comment noted. Following the final referral from the Department of Health, the appraisal will be planned into the technology appraisal schedule to allow as timely as possible guidance to the NHS.

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Additional comments on the draft remit	Rarer cancers forum	Women who develop recurrent cervical cancer generally die within 7-10 months following palliative care and this shows the need for more effective treatment	Comment noted, if the appraisal is referred it will take into account the survival of women with cervical cancer and the benefits of topotecan. No changes made to the scope.
	Welsh Assembly Government (WAG)	This regimen should be approved for use within its licensed indications. Cisplatin and topotecan is the only treatment shown to improve overall survival in recurrent cervical cancer. It is associated with a higher incidence of febrile neutropaenia (17%: probably enough to justify prophylactic use of G-CSF) compared with single agent cisplatin, but quality of life is not worse. A comparator regimen, besides cisplatin, is probably carboplatin+paclitaxel which until the publication of the results with topotecan and cisplatin was used by many in view of improved response rate and time to progression (but not overall survival).	It was agreed at the scoping workshop that the comparators should include platinum based mono and combination therapies. The has been amended in the scope

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	GSK	We have no comments on the accuracy or completeness of the background information.	Comment noted, no action required.
	RCN	The information provided is concise	Comment noted, no action required.
	RCPath	No comment	Comment noted, no action required.
	RCP	Should state the number of deaths, and number > 75 in para 4	Comment noted, the number of deaths from ovarian cancer in 2005 has been added to the scope.
	Cochrane Gynaecological Cancer Review Group	Fine	Comment noted, no action required.
	Rarer cancers forum	Correct	Comment noted, no action required.
The technology/ intervention	GSK	The description of Hycamtin for the treatment of carcinoma of the cervix is accurate.	Comment noted, no action required.
	RCPath	Yes	Comment noted, no action required.
	RCP	Yes	Comment noted, no action required.
	Cochrane Gynaecological Cancer Review Group	Fine	Comment noted, no action required.
	Rarer cancers forum	Yes	Comment noted, no action required.

Section	Consultees	Comments	Action
Population	GSK	The population is defined appropriately. As per the licensed indication, it will be necessary to consider the treatment free interval in patients with prior exposure to cisplatin within the decision problem.	Comment noted, no action required.
	RCN	Yes the population is appropriate	Comment noted, no action required.
	RCPath	Yes	Comment noted, no action required.
	RCP	Yes but… How is NICE going to appraise treatment of patients relapsing early after platinum-radiotherapy? There are no RCTs in this group and BSC alone cannot be necessarily considered the standard comparator. If NICE restricts itself to dealing only with licensed drugs then then guidance will be incomplete and not reflect the total population's needs	NICE can only issue guidance in accordance with the marketing authorisation. This specifies a sustained duration of response following cisplatin chemotherapy. It was agreed at the scoping workshop that the comparators should include platinum based mono and combination therapies. This has been amended in the scope. NICE does not require comparator drugs to be used within their marketing authorization, if they are being used as part of standard care.

Section	Consultees	Comments	Action
	Cochrane Gynaecological Cancer Review Group	OK, no specific groups	It was agreed at the scoping workshop that it was appropriate to define subgroups of patients according to the stage of disease, prior exposure to platinum based chemotherapy and duration of response to prior platinum chemotherapy.
	Rarer cancers forum	Stage IVB is a definite sub group and there should not be further sub divisions It is estimated there would only be 762 patients needing this therapy that is orphan drug status	It was agreed at the scoping workshop that it was appropriate to define subgroups of patients according to the stage of disease.
Comparators	GSK	We agree that platinum-based chemotherapy regimens are appropriate comparators for topotecan in combination with cisplatin. As various platinum based regimens are used within the NHS, the regimens to be considered in the appraisal will be specified in the decision problem. We would welcome the opportunity to discuss this further at the scoping meeting. We do not consider that best supportive care is an appropriate comparator for this appraisal. As accurately described in the background information, "In recurrent and stage IVB cervical cancer, chemotherapy will be used as palliative care when curative surgery and/or radiotherapy are unsuitable". Best supportive care would only be considered an option in patients for whom chemotherapy is unsuitable.	It was agreed at the scoping workshop that the comparators should include platinum based mono and combination therapies. This has been amended in the scope. It was agreed at the scoping workshop that BSC was not an appropriate comparator. This has been amended in the scope.
	RCPath	Yes	It was agreed at the scoping workshop that the comparators should include platinum based mono and combination therapies, but not best supportive care. This has been amended in the scope.

Section	Consultees	Comments	Action
	RCP	No; other drugs such as taxanes, gemcitabine and ifosfamide are used alone, in combinations with or without cisplatin. None of these are licensed for cervix cancer but historically have been used following evidence from phase II trials. The use of alternative chemotherapies varies across the UK, and across Europe and N Americal	It was agreed at the scoping workshop that non platinum therapies would be used in clinical practice only after the failure of platinum based chemotherapies and therefore these were not appropriate comparators for topotecan. No changes to the scope.
	Cochrane Gynaecological Cancer Review Group	One of the comparators is platinum-based chemotherapy. However, Topotecan can only be used with cisplatin (the licensed combination) in this appraisal. Paclitaxel and gemcitabine are currently often used in combination with carboplatin as it is less toxic. If there are trials of carboplatin/topotecan can these be included in the assessment?	It was agreed at the scoping workshop that the comparators should include platinum based mono and combination therapies, this could include carboplatin combinations. This has been amended in the scope.
	Rarer cancers forum	Cisplatin and best supportive care however both these as noted above need to have clear transparent and truthful models particularly the latter	It was agreed at the scoping workshop that the comparators should include platinum based mono and combination therapies, but not best supportive care. This has been amended in the scope.
Outcomes	GSK	We agree that the outcomes suggested in the draft scope capture the most important health related benefits and harms.	Comment noted, no action required.
	RCN	The outcome measures capture the benefits and harms of the proposed study.	Comment noted, no action required.
	RCPath	Yes	Comment noted, no action required.
	RCP	Yes	Comment noted, no action required.

Section	Consultees	Comments	Action
	Cochrane Gynaecological Cancer Review Group	OK, though it would have been good to see symptom control as a specific outcome as pelvic and nerve pain is a common and troublesome problem. I guess that this data will be subsumed into QoL with some loss of specific information	It was agreed at the scoping workshop that symptom control would be captured by HRQoL. No changes made to the scope.
	Rarer cancers forum	All the trails for this drug show real to women in terms of overall survival and quality of life despite the toxicity of the therapy	Comment noted, if the appraisal is referred it will take into account the survival and quality of life of women with cervical cancer. No changes made to the scope.
Economic analysis	GSK	We have no specific comments on the scope of the economic evaluation. Given the patient population, a lifetime time horizon would seem most appropriate for the analysis. We have previously constructed an economic model to assess the cost effectiveness of topotecan in this setting and would welcome the opportunity to discuss its applicability to this appraisal with NICE.	Comment noted, if the appraisal is referred to the single technology appraisal process. The manufacturer will have the opportunity to discuss the decision problem with the NICE technical team. No changes made the scope.
	RCN	The numbers of people suitable for this study maybe low for a short study so a longer time horizon should be considered.	Comment noted, the time horizon used in the appraisal will be that over which the benefits and costs can be expected to accrue. No changes made to the scope.
	RCPath	Looks appropriate	Comment noted, no action required.
	RCP	No comment	Comment noted, no action required.
	Cochrane Gynaecological Cancer Review Group	OK	Comment noted, no action required.

Section	Consultees	Comments	Action
	Rarer cancers forum	It seems that such a small population would have very little budgetary implications	Comment noted, no action required.
Equality	GSK	We do not believe that any factors exist relating to the use of topotecan for recurrent or stage IVB cervical cancer that may help promote equality and eliminate unlawful discrimination.	Comment noted, no action required.
	RCPath	No comment	Comment noted, no action required.
	RCP	Not relevant.	Comment noted, no action required.
	Cochrane Gynaecological Cancer Review Group	No issues, though this cancer is more common in the socially disadvantaged	Comment noted, no action required.
	Rarer cancers forum	As noted previously a small group of women many with very real social needs	Comment noted, no action required.
Other considerations	GSK	We do not have any additional considerations to suggest.	Comment noted, no action required.
	RCPath	None	Comment noted, no action required.
	RCP	RCTs are needed in first line therapy to reduce the recurrence rate. Pharma are unlikely to invest in licensing studies with new drugs in the population with recurrent disease as the market is small and likely to become smaller with the advent of vaccination	Comment noted, no changes made to the scope.
	Cochrane Gynaecological Cancer Review Group	None	Comment noted, no action required.
	Rarer cancers forum	Let us not have another group of patients condemned to a second rate service compared to other EU countries These women deserve so much more	Comment noted, no changes made to the scope.

Section	Consultees	Comments	Action
Questions for consultation	GSK	1. Chemotherapy regimens We would welcome the opportunity to discuss appropriate comparators for this appraisal further with NICE. Cisplatin monotherapy is the only other chemotherapeutic agent licensed to treat recurrent and stage IVB cervical cancer and we believe that cisplatin is the principal comparator for this appraisal. Platinum (cisplatin or carboplatin) based chemotherapy regimens with or without paclitaxel are routinely used for this indication. There is a disparity in clinical practice and some alternative regimens, for which the evidence base is extremely limited, may also be used rarely. We do not believe that these regimens, which include other platinum-based combinations and etoposide monotherapy, represent appropriate comparators for this appraisal. 2. Best supportive care As stated previously, we do not believe that best supportive care is an appropriate comparator for this appraisal. 3. Subgroups We believe that patients' prior cisplatin use and duration of response to prior platinum therapy may influence the clinical and cost-effectiveness of topotecan in combination with cisplatin and would welcome the opportunity to discuss this further with NICE. 4. Discriminatory and equality issues As stated previously, we do not believe that any issues with respect to treatment with topotecan + cisplatin require special attention in light of the duty to have due regard to the need to eliminate unlawful discrimination. 5. Appraisal process As cisplatin is the only alternative treatment licensed for this indication, we believe that the single technology appraisal process is the most suitable for appraising topotecan in combination with cisplatin	Comment noted, if the appraisal is referred to the single technology appraisal process. The manufacturer will have the opportunity to discuss the decision problem with the NICE technical team. It was agreed at the scoping workshop that the comparators should include platinum based mono and combination therapies, but not best supportive care. This has been amended in the scope. It was agreed at the scoping workshop that it was appropriate to define subgroups of patients according to the stage of disease, prior exposure to platinum based chemotherapy and duration of response to prior platinum chemotherapy. It was agreed at the scoping workshop that there were no specific equalities issues. It was agreed at the scoping workshop that topotecan could be appropriately appraised through the single technology appraisal process.

Section	Consultees	Comments	Action
	RCPath	Question 1 - already covered. Questions 2 to 4 - best covered by experts in the field of Oncology.	Comments noted, please see previous responses.
	RCP	There are no RCTs of BSC, so taking BSC alone as the comparator does not seem appropriate. However, NICE does not consider drugs not used in licence which will make the guidance a little artficial	It was agreed at the scoping workshop that BSC was not an appropriate comparator. This has been amended in the scope. NICE does not require comparator drugs to be used within their marketing authorization, if they are being used as part of standard care.
	Cochrane Gynaecological Cancer Review Group	No identifiable groups likely to benefit more or less from such treatment	It was agreed at the scoping workshop that it was appropriate to define subgroups of patients according to the stage of disease, prior exposure to platinum based chemotherapy and duration of response to prior platinum chemotherapy.
Additional comments on the draft scope.	GSK	No additional comments.	Comment noted, no action required.
	Cochrane Gynaecological Cancer Review Group	None	Comment noted, no action required.

Comment 4: Regulatory issues

Section	Consultees	Comments	Action
Remit			No comments received.

Section	Consultees	Comments	Action
Current or proposed marketing authorisation	GSK	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.	Comment noted, no action required.

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

Macmillan Cancer Support
NHS QIS
Royal Pharmaceutical Society